

Exhibit 8

Lembke Report

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EXPERT REPORT, ANNA LEMBKE, M.D.

August 1, 2020

RELATING TO

Cabell County Commission and City of Huntington, West Virignia, (The Cabell Huntington Community) v. AmerisourceBergen Drug Corporation, Cardinal Health, Inc., and McKesson Corporation,

No. 1:17-op-45053-DAP and No. 1:17-op-45054

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A. Background and Qualification

1. I am an Associate Professor, Chief of the Addiction Medicine Dual Diagnosis Clinic, Medical Director of Addiction Medicine, and Program Director of the Addiction Medicine Fellowship, in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. Since 2016, I also hold a Courtesy Appointment in the Stanford University Department of Anesthesiology and Pain Medicine. I began my faculty career at Stanford in 2003. A true copy of my current CV is attached to this Report as Exhibit A.

2. I received my undergraduate degree in Humanities from Yale University in 1989, and my medical degree from Stanford University in 1995, where I also completed a partial residency in Pathology (1997) and a full residency in Psychiatry (2000), as well as a Fellowship in Mood Disorders, Department of Psychiatry and Behavioral Sciences (2002).

3. I have been licensed to practice medicine in the State of California from 1995 to the present. I received the DEA-X waiver to prescribe buprenorphine products in 2013. I am a diplomate of the American Board of Psychiatry and Neurology (2003; recertified, 2013), and a diplomate of the American Board of Addiction Medicine (2013).

4. From 2001 to the present, I have taught medical students, residents, and fellows at Stanford University School of Medicine, on a diversity of topics related to psychiatry, addiction, and pain. For example, from 2004 to the present, I have given annual lectures on addiction medicine within the Practice of Medicine (POM) series for Stanford medical students, including topics such as the neurobiology of addiction, how doctors should intervene when they detect substance use problems, and how to have difficult conversations with patients on the topic of substance use, misuse, overuse, and addiction.

5. I received the Stanford Award for Excellence in Academic Teaching, Department of Psychiatry, in 2014, and again in 2018.

6. In 2013 I founded and became the Training/Program Director for Stanford's Addiction Medicine Fellowship, a post-graduate sub-specialty training year in the treatment of addiction for any medical graduate of a U.S. or Canadian medical school and ACGME-accredited residency. In 2020 I was awarded the ASAM Training Directors Award "for outstanding training in the evaluation, treatment, research and teaching of substance use disorders."

7. As a full time faculty at the Stanford University School of Medicine, I regularly treat patients with addiction to opioids and other substances. For the last 15 years, my clinical practice has included a significant proportion of patients taking prescription opioids for pain relief, for whom such drugs have resulted in misuse, dependence, and addiction. As an integral part of my practice, I work with these patients to develop treatment plans that will address their pain while making appropriate efforts to reduce (taper) or eliminate use of opioids, and/or treat

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their opioid addiction. Such plans can include non-opioid medications for pain, as well as alternative, non-pharmaceutical modalities, and counseling, with a dual focus on treating the underlying painful condition and the substance use disorder. I frequently collaborate with pain and primary care colleagues concerning populations with chronic pain and substance use disorders.

8. In 2015, I received the Stanford Chairman's Award for Clinical Innovation for developing inpatient and outpatient clinical services dedicated to helping people with substance use problems.

9. In January 2015, I was appointed by Governor Jerry Brown to the Research Advisory Panel of California. I served on the Panel until 2017. I, along with the other Panel members, was tasked with assessing the safety of clinical trials to be conducted in the state of California using controlled substances, such as opioids. In this capacity, I applied my knowledge and experience to the review of study designs and protocols, and I made recommendations for procedures to protect patients in these trials, including, in particular, protection from potential harmful effects of opioids.

10. From 2015 to 2019, I served on the Board of the California Society of Addiction Medicine (CSAM). I have been a member of CSAM, and the American Society of Addiction Medicine (ASAM), since 2011.

11. In 2015-2016 I chaired the Planning Committee for the California Society of Addiction Medicine (CSAM) Annual Addiction Medicine Conference.

12. In 2016, I became president of the Addiction Medicine Fellowship Directors Association (AMFDA).

13. In 2016, I led a program funded by the Stanford Center for Continuing Medical Education (SCCME), titled, "Tapering Patients Off of Chronic Opioid Therapy."¹

14. Since 2016, I have chaired the Addiction Medicine Task Force, Stanford University School of Medicine. The goal of the Task Force is to re-evaluate and re-create the medical school curriculum on addiction and safe prescribing of addictive substances. I have served as MedScholar Advisor on the topic of *Developing the Addiction Curriculum at Stanford*,

¹ *How to Taper Patients Off of Chronic Opioid Therapy*, Stanford University School of Medicine, <https://med.stanford.edu/cme/courses/online/opioid-taper.html>. Chronic pain is frequently considered to be pain that lasts longer than 3 months. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 2016;15(15):1624–1645, at p. 1625.

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Stanford University School of Medicine. The new medical school curriculum we have created includes didactics on the neurobiology of addiction, the treatment of addiction, the management of opioid prescribing in the setting of chronic pain, and the history and origins of the opioid epidemic.

15. In 2019, the Stanford Center for Health Education asked me to lead and design an online course on addiction for Stanford learners all over the world. I am in the process of developing this course, called “Psychology of Addiction and Recovery.” This course explores changing concepts of addiction through time, risk factors for addiction, and treatments for addiction including biological, psychological and public policy approaches. The course will be available beginning in August 2020.

16. I am the author of a book on the prescription drug epidemic: *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* (Johns Hopkins University Press, 2016),² highlighted in the *New York Times* as one of the top five books to read to understand the opioid epidemic.³

17. I have published over 100 peer-reviewed articles, chapters, and commentaries, which have appeared in the *New England Journal of Medicine*, *Journal of the American Medical Association*, *Pain Medicine*, *Journal of General Internal Medicine*, *Addiction*, and other peer reviewed journals. Many of these publications address the diagnosis and treatment of addiction, as well as the treatment of pain. I have also published articles on the importance of teaching addiction medicine in medical school, residency, and fellowship.

18. In 2016, I co-authored a peer-reviewed article, “Weighing the Risks and Benefits of Chronic Opioid Therapy,” which addressed issues of opioid misuse and addiction, risk assessment and mitigation, patient education, tapering to reduce or end opioid exposure, tolerance, dependence, and risks of overdose.⁴ *American Family Physician* is among the most read family physician peer reviewed journals. The readership includes 32,000 medical students and over 3,700 nurse practitioner and physician assistant subscribers.

19. In 2016, I co-authored a Research Letter in *JAMA Internal Medicine* which examined Medicare data on opioid drug prescription patterns. Our analysis concluded that opioid prescribing is “a widespread practice relatively indifferent to individual physicians, specialty or

² Lembke, Anna. *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why Its so Hard to Stop*. Johns Hopkins University Press, 2016.

³ Abigail Zuger, *A Doctor's Guide to What to Read on the Opioid Crisis*, N.Y.Times (Dec. 17, 2018)

⁴ Lembke A, Humphreys K, Newmark J. Weighing the risks and benefits of chronic opioid therapy. *Am Fam Physician*. 2016; 93(12):982-990.

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region. High-volume prescribers are not alone responsible for the high national volume of opioid prescriptions. Efforts to curtail national opioid overprescribing must address a broad swath of prescribers to be effective.”⁵ This article has been cited 108 times in the 4 years since its publication,⁶ and demonstrates that the epidemic of opioid drug misuse and addiction is attributable to many prescribers, including but not limited to high-frequency prescribers, who are sometimes referred to as “pill mills.”

20. In 2016, I co-authored a Research Letter in *JAMA Psychiatry* on the high exposure to opioids among Medicare patients, the growing incidence of opioid use disorder in this population, and the lack of buprenorphine prescribers in this population, noting the gap between the need for treatment, and access to that treatment.⁷

21. In 2018, I co-authored two articles in peer-reviewed pain journals on pain management of patients with chronic pain and opioid use disorder.^{8,9}

22. In 2019, I co-authored two articles in peer-reviewed journals on how to transition hospitalized patients with acute or chronic pain onto opioid agonist treatment while still managing pain.¹⁰ Opioid agonist treatment refers here to buprenorphine, an opioid used to treat severe opioid use disorder, but which can be difficult to initiate due to its unique chemical properties.

⁵ Chen JH, Humphreys K, Shah NH, Lembke A. Distribution of opioids by different types of medicare prescribers. *JAMA Intern Med.* December 2015;1-3. <http://dx.doi.org/10.1001/jamainternmed.2015.6662>, at pp. 260-261.

⁶ “Distribution of opioids by different types of medicare prescribers” Google Scholar Results https://scholar.google.com/scholar?cites=3449278328675579417&as_sdt=2005&sciodt=0,5&hl=en (last accessed April 14, 2020)

⁷ Lembke A, Chen JH. Use of opioid agonist therapy for medicare patients in 2013. *JAMA Psychiatry*. 2016;73(9). doi:10.1001/jamapsychiatry.2016.1390.

⁸ Harrison TK, Kornfeld H, Aggarwal AK, Lembke A. Perioperative Considerations for the Patient with Opioid Use Disorder on Buprenorphine, Methadone, or Naltrexone Maintenance Therapy. *Anesthesiol Clin.* 2018;36(3):345-359. doi:10.1016/j.anclin.2018.04.002.

⁹ Lembke A, Ottestad E, Schmiesing C. Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period. *Pain Med.* 2018;(February):1-4. doi:10.1093/pmt/pny019.

¹⁰ Raheemullah, A., Lembke, A. Initiating Opioid Agonist Treatment for Opioid Use Disorder in the Inpatient Setting: A Teachable Moment, *JAMA Internal Medicine*, 2019; 179(3):427-428. Raheemullah, A., Lembke, A. Buprenorphine Induction Without Opioid Withdrawal: A Case Series of 15 Opioid-Dependent Inpatients Induced on Buprenorphine Using Microdoses of Transdermal Buprenorphine. *American Journal of Therapeutics*, 2019; 0:1-7.

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23. In 2018 and 2020, I co-authored two articles in peer-reviewed journal on the risks of opioid and benzodiazepine co-prescribing.¹¹

24. I have devoted a significant portion of my professional career to the development of patient-centered protocols to reduce or discontinue opioid use among individuals for whom the risks of prescription opioids outweigh the benefits, including publication of such protocols for use by other clinicians, and my work in this area has been recognized by leading authorities. I have created a Stanford-supported, free, online, continuing medical education course on how to taper opioids in patients with chronic pain <https://med.stanford.edu/cme/courses/online/opioid-taper.html>. In September 2019, the United States Department of Health and Human Services (HHS) issued the HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics. On October 10, 2019, the *Journal of the American Medical Association* (JAMA) published a commentary about the HHS Guidelines, authored by officials of the United States Centers for Disease Control and the National Institute on Drug Abuse.¹² Authors of the HHS Guidelines asked for permission to include a decision-making “flow chart” from an article that I co-authored in the *Annals of Internal Medicine* in August 2019; that permission was granted, and the HHS Guidelines included an adaptation of our published decision tree, providing recommendations on how and when to taper patients from long-term opioid use.¹³ In addition, in January 2020, *American Family Physician* published my article, “Tapering Long-Term Opioid Therapy,” which was offered to professionals for 6 hours of Continuing Medical Education (CME) credit, further documenting the acceptance of my work in this area.¹⁴

25. I have testified before the United States House of Representatives on the opioid epidemic and possible means to mitigate harms caused by that epidemic, and I have presented at

¹¹ Lembke, A., Papac, J., Humphreys, K. Our Other Prescription Drug Problem, *N Engl J Med* 2018; 378(8):693-695; Azad, Lembke, A. et al, Patterns of Opioid and Benzodiazepine Use in Opioid-Naïve Patients with Newly Diagnosed Low Back and Lower Extremity Pain, , *J Gen Intern Med*, 2019, 35(1):291-297. doi: 10.1007/s11606-019-05549-8.

¹² Dowell, et al., Patient-Centered Reduction or Discontinuation of Long-Term Opioid Analgesics. *JAMA*. 2019;322(19):1855-1856. doi:10.1001/jama.2019.16409; Chou, et al., Rethinking Opioid Dose Tapering, Prescription Opioid Dependence, and Indications for Buprenorphine, *Ann Intern Med*. 2019;171(6):427-429; United States Department of Health and Human Services. HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-term Opioid Analgesics. (October 2019); https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf at p. 3.

¹³ Chou, et al., Rethinking Opioid Dose Tapering, Prescription Opioid Dependence, and Indications for Buprenorphine, *Ann Intern Med*. 2019; 171(6):427-429. As discussed in this Report, it is essential to patients’ well-being that proper, patient-centered methods of tapering are followed, to reduce or eliminate opioid use without imposing unnecessary risks associated with rapid or formulaic discontinuation of these drugs.

¹⁴ Lembke A., Tapering Long-Term Opioid Therapy. *Am Fam Physician* 2020; 101(1):49-52.

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numerous conferences before governmental, professional, academic and lay audiences on related topics.

26. Since the publication of my book, *Drug Dealer, MD*, I have been invited to make presentations to doctors, legislators, and the public, regarding the causes of the opioid epidemic and how we can combat it. A significant portion of my work in this area consists of describing the false and misleading messages promoted by the Pharmaceutical Opioid Industry as detailed in this Report, including but not limited to false representations of the risk of addiction, unsupported claims of long-term efficacy for chronic pain, downplaying the risks of dependence and withdrawal, and misinforming doctors about the extent to which opioid doses could safely be increased. As to all of these subjects, it has been my experience that audiences of professionals and lay persons alike continue to be misled by the decades-long campaign of misinformation promoted through the Industry's marketing of opioids. "Academic detailing" is the process of providing accurate information to medical providers about the risks and benefits of a drug, to balance and re-educate after exposure to one-sided and inaccurate messaging from the detailers who have conveyed Industry messages to those providers over extended periods of time. As noted by the Report of the Association of Schools and Programs of Public Health (ASPPH), issued in November 2019, there is a need for "*extensive academic detailing and counter-detailing on opioids*" to correct the inaccurate and misleading claims previously made by the companies that manufacture those drugs, messages that continue to confuse or mislead some patients and prescribers.¹⁵ I began and performed my work in academic detailing before any connection or thought of involvement in litigation, and I continue in this role to counter the false and misleading marketing messages of the Pharmaceutical Opioid Industry.

27. In forming the opinions expressed in this Report, I have relied on my medical training, more than twenty years of clinical experience, and my own research on opioid prescribing. My research began circa 2001 and has been multimodal. I have done qualitative interviews with patients, providers, and others in the health care field on questions related to opioid prescribing. I have followed and analyzed the medical literature using PubMed and other academic search engines, along with different combinations of key words such as "pain, opioids, treatment, randomized clinical trials, open label trials, effectiveness, adverse effects, prescribing, addiction, dependence, overdose, etc. ..." I have compiled statistics published by the CDC and other government agencies. I have, in collaboration with colleagues, analyzed opioid prescribing databases such as Medicare Part D.^{16,17} As a regular and ongoing part of my practice, I conduct

¹⁵ Association of Schools & Programs of Public Health (ASPPH) Report, "Bringing Science to Bear on Opioids," 11/01/2019, at p. 21.

¹⁶ Chen *et. al.*, "Distribution of Opioids," fn. 5, above, at p. 259.

¹⁷ Lembke, *et al.*, "Use of Opioid Agonist Therapy," fn. 7, above, at p. 990.

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literature searches of research on the subjects of addiction and pain treatment, which is essential to my work with my patients. Indeed, given the large and increasing role of opioid drugs in addiction, the fields of addiction and pain medicine are inevitably intertwined, such that it is essential to my practice to remain aware of the state of scientific inquiry in both fields. Specifically for this Report, I have considered the materials listed in Exhibit B, attached. I hold the opinions stated in this Report to a reasonable degree of scientific certainty.

28. Attached as Exhibit A is a copy of my current curriculum vitae and a list of all publications authored by me in the past 10 years.

29. Attached as Exhibit B is a list of data or other information considered by me in forming the opinions expressed herein.

30. Attached as Exhibit C is a statement of my compensation for services performed in this case.

31. Attached as Exhibit D is a list of all cases in which I have testified as an expert at trial or by deposition during the past four years.

B. Opinions

For the reasons set forth in detail in this Report, I hold the following opinions:

1. The addictive nature of medicinal opioids has been known for centuries. The Pharmaceutical Opioid Industry's misrepresentations of the safety and efficacy of prescription opioids reversed a century of appropriate restrictions on the use of these dangerous drugs, and substantially contributed to the current opioid epidemic.

2. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. When supply of an addictive drug is increased, more people become addicted to and suffer the harms of that drug. Prescription opioids are as addictive as heroin, and the Defendants' conduct in promoting increased supply and widespread access to prescription opioids has resulted in an epidemic of opioid addiction and overdose death.

3. Opioid prescribing began to increase in the 1980's and became prolific in the 1990's and the early part of the 21st century, representing a radical paradigm shift in the treatment of pain, and creating more access to opioids across the United States.

4. The Pharmaceutical Opioid Industry contributed substantially to the paradigm shift in opioid prescribing through misleading messaging about the safety and efficacy of prescription opioids. The Industry disseminated these misleading messages through key opinion leaders, medical school curricula, continuing medical education courses, clinical decision support tools, professional medical societies, the Federation of State Medical Boards, and the Joint Commission.

5. Opioid distributors collaborated with opioid manufacturers and pharmacies to promote sales of opioid pain pills. Such coordinated efforts included programs to give away free samples of opioids; coupons to discount opioids; and promotion of specific opioid products under the guise of education. These activities increased the population of opioid users, dose and duration of opioid use, and the risk of opioid misuse, addiction, dependence, and death.

6. No reliable scientific evidence shows that long-term opioid therapy is effective for chronic non-cancer pain.

7. The Pharmaceutical Opioid Industry misrepresented that the risk of addiction to prescription opioids is "rare," or "less than 1%," when in fact prescription opioids are as addictive as heroin, and the risk of addiction is far higher than stated by the Industry. The best, conservative data show an opioid addiction prevalence of 10-30% among chronic pain patients prescribed opioids.

8. Increased supply of prescription opioids contributed substantially to more individuals becoming addicted to opioids and transitioning from prescription opioids to illicit sources of opioids such as heroin and fentanyl (The Gateway Effect).

9. Increased supply of prescription opioids contributed substantially to more individuals, including newborns, becoming dependent on opioids, increasing their risk for opioid-related morbidity and mortality (The Dependence Effect).

10. Increased supply of prescription opioids contributed substantially to diversion of prescription opioids to individuals for whom they had not been prescribed (The Tsunami Effect).

11. The increased supply of prescription opioids through licit and illicit sources resulted in a prescription opioid epidemic in the United States. "Epidemic,"

defined as an outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990's and continuing to the present day.

12. Today's opioid crisis would not have occurred without the overprescribing and excessive supply of opioids, which together contributed substantially to the scourge of addiction and death.

13. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.

C. Detailed Statement of Opinions

1. The addictive nature of medicinal opioids has been known for centuries. The Pharmaceutical Opioid Industry's misrepresentations of the safety and efficacy of prescription opioids reversed a century of appropriate restrictions on the use of these dangerous drugs, and substantially contributed to the current opioid epidemic.

- a. Opioids are among the world's oldest known drugs. Use of opium from the poppy plant for medical, recreational, and religious purposes can be traced throughout history and across continents, beginning in the 4th century B.C.¹⁸
- b. In the 19th century, two major scientific advances in medicinal opioids had far-reaching consequences. In 1804, German pharmacist Friedrich Sertürner isolated morphine, an opioid alkaloid derived from opium and ten times as potent.¹⁹ In 1855, Alexander Wood invented the hypodermic syringe, making possible fast easy administration of morphine.²⁰

¹⁸ Lembke A. Psychology of Addiction and Recovery. Lecture: History of Addiction (Stanford University, Fall/Winter 2020).

¹⁹ Meldrum ML. A capsule history of pain management. *JAMA*. 2003;290:2470-2475, at p. 2471

²⁰ Lembke, "Drug Dealer MD", fn 2, above, at p. 42. See also Meldrum, "Capsule history", fn. 19, above, at p. 2471.

- c. It was assumed (wrongly) that opioids administered by a doctor using a hypodermic syringe would not be addictive. During the Civil War, opium, laudanum and hypodermic morphine were used extensively to treat soldiers and Victorian housewives alike. Hypodermic morphine soon became the major driver of American's first opioid epidemic. Hundreds of reports in late nineteenth century medical journals detailed iatrogenic (physician-initiated) cases of morphine addiction. The risk of addiction increased in cases where doctors continued to administer hypodermic morphine over long periods of time for protracted illnesses.²¹ The two most important risk factors were exposure to opioids and a history of chronic illness. In the 1870s and 1880s, America's per capita consumption of opioids tripled.²²
- d. The opioid addiction epidemic of the late 19th and early 20th century led to ever-stricter laws and regulations regarding the prescribing and dispensing of opioids in medical practice.²³ As a result, the first several decades of the 1900s saw a steady decrease in the per capita consumption of medicinal opioids.²⁴
- e. Medical training and education throughout the 20th century, save for the last two decades, was filled with warnings about the addictive potential of medicinal opioids, even to patients with severe pain and dire illness, but especially when used long term in the treatment of chronic pain. Physicians were urged to use opioids sparingly, for short duration, and only in cases of severe trauma and at the end of life.²⁵ For example, a peer-reviewed study published in 1954 concluded "Morphine is not the answer to chronic pain. Because of the development of tolerance to the analgesic effects of morphine, alleviation of pain becomes inadequate. Under such circumstances the physician, by gradually withdrawing narcotics, does not deprive the patient of any actual benefit but protects him and his family from the possible legal, social, or economic difficulties attendant on opiate addiction. The administration of morphine to a patient with chronic pain is a short-lived type of kindness. Long-term kindness

²¹ Courtwright DT. "Dark Paradise: A History of Opiate Addiction in America". Harvard University Press; 2001, at pp. 46-47.

²² *Id.* at pp. 2-3 and 62-63.

²³ Lembke, "Drug Dealer MD", fn. 2, above, at footnote p. 57.

²⁴ Courtright, "Dark Paradise", fn. 21, above, at p. 29

²⁵ Lembke, "Drug Dealer MD", fn. 2, above, at pp. 56-57.

would begin when opiates are withheld or withdrawn in favor of other therapeutic measures.”²⁶

- f. The current opioid epidemic in the United States, occurring almost exactly 100 years after the first major opioid epidemic, was ushered in by the reversal of a century of prudential legislation and medical training. The result, since the 1990s, has been a prolonged period of opioid overprescribing with concomitant opioid addiction, dependence, and overdose death. When Defendants claim that knowledge of the addictive potential of medicinal opioids is new, they ignore 100 years of medical experience, knowledge, and legislation.²⁷ The addictive nature of medicinal opioids has been known for centuries.

2. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. When supply of an addictive drug is increased, more people become addicted to and suffer the harms of that drug. Prescription opioids are as addictive as heroin, and the Defendants' conduct in promoting increased supply and widespread access to prescription opioids has resulted in an epidemic of opioid addiction and overdose death.

- a. Addiction is the continued use of a substance despite harm to self and others and/or a desire to quit or cut back. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) uses the term “substance use disorder” to denote addiction. I use the terms “opioid addiction” and “opioid use disorder” interchangeably here.

²⁶ Rayport M. Experience in the Management of Patients Medically Addicted to Narcotics. *JAMA - J Am Med Assoc.* 1954;156(7):684-691, at p. 690.

²⁷ Lembke, “Drug Dealer MD”, fn. 2, above, at pp. 56-57

- b. DSM-5 denotes 11 different criteria to diagnose opioid use disorder (OUD)²⁸. A short-hand way to remember these criteria is the “four C’s”: Control, Compulsion, Craving, and continued use despite Consequences.
 - i. Control refers to out-of-control use, for example using more than intended, or an inability to cut back use when necessary.
 - ii. Compulsion refers to mental preoccupation with using against a conscious desire to abstain.
 - iii. Craving refers to physiologic and/or mental states of wanting.
 - iv. Consequences refers to the social, legal, economic, interpersonal, and other problems that arise as a result of use, yet which still do not deter use.
- c. The physiological phenomena of tolerance and withdrawal are included in the DSM-5 criteria, but they are not required in order to make the diagnosis of opioid use disorder/addiction. In other words, tolerance and withdrawal are recognized as separate physiologic phenomena often seen in addiction, but not definitional for addiction. Further, under DSM-5, the criteria of tolerance and withdrawal do not count toward a diagnosis of addiction when a patient is prescribed opioids under the supervision of a doctor, making it more difficult to diagnose addiction to prescription opioids. As discussed later in this Report, Defendants influenced this definition by characterizing dependence as a benign condition entirely separate from addiction. In reality, dependence, withdrawal, and tolerance are closely linked to the disease of addiction, and from a neurobiological perspective, may be identical phenomena.
- d. The DSM-5 also recognizes that addiction is a spectrum disorder, divided into mild, moderate, and severe, based on the number of criteria met.²⁹
- e. The American Society of Addiction Medicine (ASAM) has defined addiction as follows: “Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these

²⁸ *Diagnostic and Statistical Manual of Mental Disorders*. (DSM-5) Washington, DC: American Psychiatric Association; 2013 at p. 541.

²⁹ *Id.* at pp. 541-542.

circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.”³⁰ This ASAM definition of addiction is consistent with but not identical to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The ASAM definition does not single out any specific substance, highlighting the idea that all addictive drugs work on the same common brain pathway.

- f. From a neuroscience perspective, addiction is a disorder of the brain’s reward circuitry.³¹
 - i. Opioids, in addition to binding the *mu*-pain receptors, also cause the release of the neurotransmitter dopamine. In order to accommodate the high amount of dopamine released, the brain adapts by downregulating its own endogenous dopamine and its own endogenous dopamine receptors. This process is called neuroadaptation, and the result is a dopamine deficit state, wherein the threshold for experiencing pleasure goes up, and the threshold for experiencing pain goes down. Addicted individuals then need the substance not to feel good, but to escape the pain of withdrawal.
 - ii. In severe forms of addiction, individuals commit all available resources to obtaining more of the substance, even forgoing natural rewards like food, finding a mate, or raising children.³² By

³⁰ American Society of Addiction Medicine (ASAM) Definition of Addiction.

<https://www.asam.org/resources/definition-of-addiction>; accessed June 20, 2018, at p. 1.

³¹ Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010;35:217-238. doi:10.1038/npp.2010.4.

³² Schultz W. Potential vulnerabilities of neuronal reward, risk, and decision mechanisms to addictive drugs. *Neuron*. 2011;69(4):603-617. doi:10.1016/j.neuron.2011.02.014.

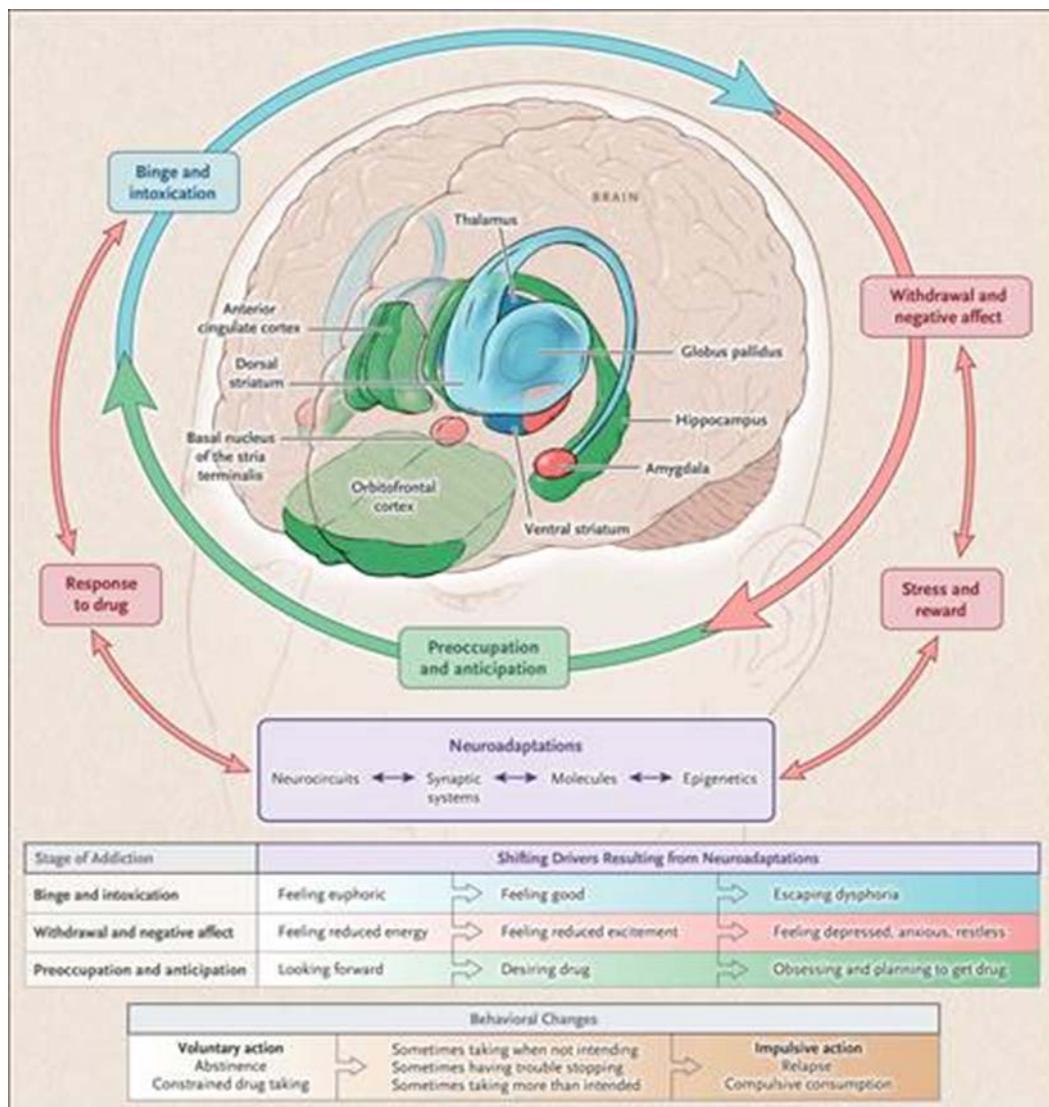
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hijacking the brain's reward and motivational centers, addiction leads to compulsive, self-destructive consumption that overcomes the limits of voluntary choice. The cycle of neuroadaptation is illustrated below³³:

³³ Volkow, ND., et al., Neurobiologic Advances from the Brain Disease Model of Addiction. *N Engl J Med.* 2016; 374:363-371, Figure 1.

Cycle of Neuroadaptation³⁴



- g. Because addiction affects the same neural pathways evolved over millions of years to encourage humans to seek out pleasure and avoid pain, everyone is vulnerable to the disease of addiction.

³⁴ *Id.*

- i. Or as Nora Volkow, Director of the National Institute on Drug Abuse, and Thomas McLellan, former Deputy Director of the Office of National Drug Control Policy, wrote in their review “Opioid Abuse in Chronic Pain” in the New England Journal of Medicine (2016), “no patient is immune to addiction.”³⁵ Similarly, as stated by the CDC, “Anyone who takes prescription opioids can become addicted to them.”³⁶
- ii. Without activation by consumption of the drug, the disease of addiction does not exist. This is supported by studies that have identified a dopamine receptor deficit state among those exposed to addictive drugs, compared to healthy subjects who have not been exposed, as illustrated below.³⁷

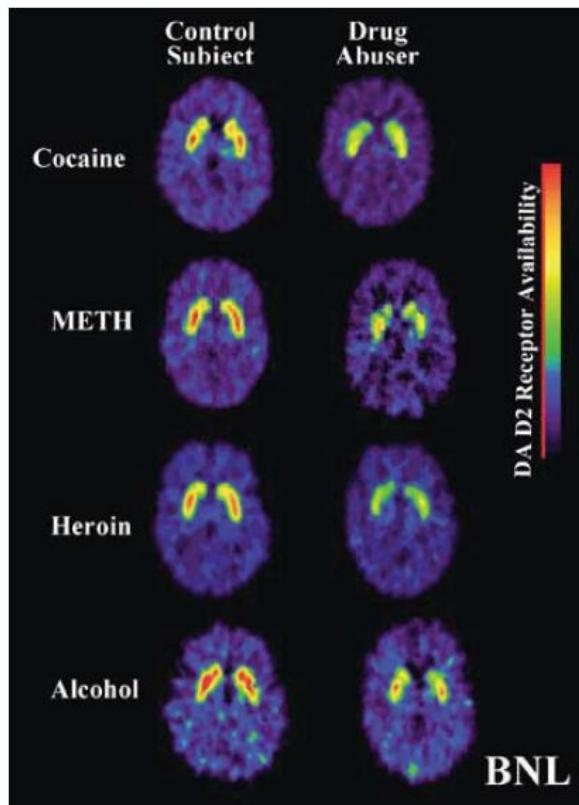
³⁵ Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain - Misconceptions and Mitigation Strategies. *N Engl J Med.* 2016;374(13):1253-1263. doi:10.1056/NEJMra1507771, at p. 1254.

³⁶ Centers for Disease Control and Prevention. *Prescription Opioids.*

<https://www.cdc.gov/drugoverdose/opioids/prescribed.html> (last updated August 29, 2017)

³⁷ Koob *et.al.*, “Neurocircuitry,” fn.31, above, p. 223; Volkow ND, Fowler JS, Wang G-J, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry.* 2004;9(6):557-569. doi:10.1038/sj.mp.4001507 at p. 557.

The Effect of Addiction on Dopamine Receptors³⁸



- h. Exposure to/consumption of the addictive substance is a necessary criterion for the development of addiction to that substance. One of the biggest risk factors for becoming addicted to a substance is simple exposure to that substance.
- i. The current opioid epidemic is a tragic and compelling example of increased access leading to increased addiction and related death. The nearly quadrupling of opioid prescribing between 1999 and 2012, combined with widespread distribution of those opioids to every corner of America, does not merely correlate with rising rates of opioid addiction and related deaths, it is causative.

³⁸ Volkow ND, Fowler JS, Wang GJ, Swanson JM, Telang F. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. *Arch Neurol.* (2007) 64:1575–9. 10.1001/archneur.64.11.1575 at p. 6.

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- i. A Task Force appointed by the Association of Schools and Programs in Public Health (ASPPH), issued a Report on November 1, 2019, concluding, “The *tremendous expansion of the supply* of powerful (high-potency as well as long-acting) prescription opioids led to scaled increases in prescription opioid dependence, and the transition of many to illicit opioids, including fentanyl and its analogs, which have subsequently driven exponential increases in overdose.”³⁹ The report also stated that addiction, or Opioid Use Disorder, “is caused by repeated exposure to opioids.”⁴⁰ ASPPH consists of over 120 member institutions accredited by the Council on Education for Public Health, including including the West Virginia University School of Public Health .⁴¹ The Task Force was appointed by the ASPPH board of directors, and was composed of 14 “recognized experts in the field.” I agree with these statements of the ASPPH Task Force, which are consistent with, and supportive of, the opinions I have expressed in this Report, and in my work prior to becoming involved in litigation related to the opioid epidemic.
- ii. In their 2017 report “Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use,” The National Academies of Science, Engineering and Medicine (NASEM) cited “heavy promotion of opioid prescribing by drug manufacturers (including misleading claims by some) and substantially increased prescribing” as contributors to the widespread availability and exposure to prescription opioids.⁴²
- iii. The NASEM Report also found that diversion is a key contributor to increased exposure to prescription opioids. Prescription drugs are diverted to nonmedical use in several ways: (1) diversion before a prescription has been filled (*e.g.*, theft from production

³⁹ ASPPH Report, “Bringing Science to Bear on Opioids,” fn.15, above, at p. 8 (emphasis added).

⁴⁰ *Id.*at p. 10.

⁴¹ *Id.*at pp. 2-3, 56.

⁴²National Academies of Science Engineering and Medicine (NASEM). *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*; 2017. doi:10.17226/24781, at pp. 40-41 (emphasis added).

facilities or retail pharmacies), (2) diversion via the filling of a prescription (*e.g.*, pursuant to doctor shopping and high-frequency prescribers, etc.) and (3) diversion after a prescription has been filled (*e.g.*, by subsequent transfer or sale to a third party). “The DEA (2016b, p. 34) reports that in recent years, distributors in the United States disbursed 12–15 billion dosage units of opioid narcotics to retail-level purchasers, suggesting that total diversion is on the order of 2.5–4.0 billion dosage units.”⁴³ A *Washington Post* analysis of federal ARCOS data shows that from 2006-2014, more than 100 billion oxycodone and hydrocodone pills were delivered in the United States.⁴⁴ At the same rate of diversion reported by NASEM for the period it reviewed, that would represent diversion on the order of 15.8-25 billion pills during the nine year period from 2006-2014.

- iv. Likewise, decreased supply of addictive substances decreases exposure and risk of addiction and related harms. Two natural experiments in the last century tested and proved this hypothesis. The first was Prohibition, a nationwide constitutional ban on the production, importation, transportation, and sale of alcoholic beverages from 1920 to 1933, which led to a sharp decrease in the number of Americans consuming and becoming addicted to alcohol.⁴⁵ (There were other unintended consequences of Prohibition, but the positive impact on alcohol consumption and related morbidity is widely under-recognized.) Second, many soldiers in Vietnam during the Vietnam War became addicted to opioids, most of whom stopped using opioids on their return to the United States, where access was limited.⁴⁶
- j. Opioids are different from other addictive substances for the following reasons:

⁴³ *Id.* at p. 223.

⁴⁴ Steven Rich, Scott Higham and Sari Horwitz *More than 100 Billion Pain Pills Saturated the Nation over Nine Years*, Washington Post, January 14, 2020.

⁴⁵ Hall W. What are the policy lessons of National Alcohol Prohibition in the United States, 1920-1933? *Addiction*. 2010. doi:10.1111/j.1360-0443.2010.02926.x, at p. 105.

⁴⁶ Robins LN, Davis DH, Nurco DN. How permanent was Vietnam drug addiction? *Am J Public Health*. 1974;64(12 Sup):38-43. doi:10.2105/AJPH.64.12_Suppl.38, at p. 40.

- i. They are sold as medicine, normalizing their use and propagating a misleading safety profile, with devastating consequences.
- ii. They kill quickly, such that even a single exposure in an opioid naïve person can lead to death.
- iii. They create a debilitating dependence such that painful withdrawal leads to a vicious cycle of drug-seeking and withdrawal, as discussed in Section 9 of this Report, below.

3. Opioid prescribing began to increase in the 1980's and became prolific in the 1990's and the early part of the 21st century, representing a radical paradigm shift in the treatment of pain, and creating more access to opioids across the United States.

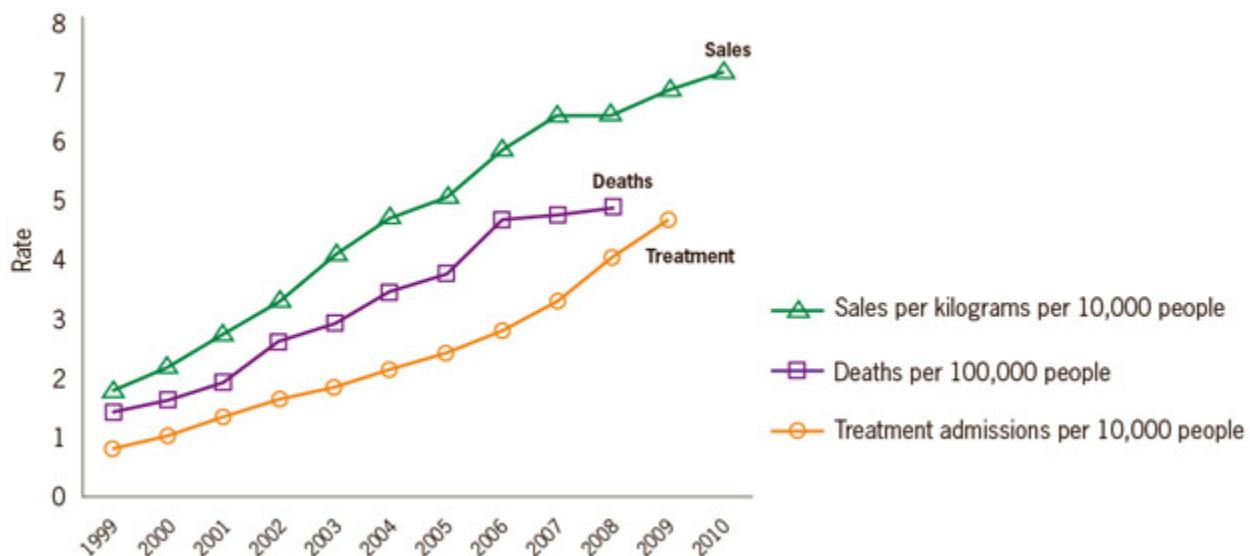
- a. Prior to 1980, doctors used opioid pain relievers sparingly, and only for the short term in cases of severe injury or illness, during surgery, or at the very end of life.⁴⁷ Doctors' reluctance to prescribe opioids stemmed from the legitimate concern that patients would get addicted.
- b. Opioid prescribing tripled between the 1990's and 2012, and dramatically increased in dose and duration. "By 2010, enough OPR [opioid pain relievers] were sold to medicate every American adult with a typical dose of 5 mg of hydrocodone every 4 hours for 1 month."⁴⁸
 - i. From 1996 to 2011 there was a 1,448% increase in the medical use of opioids, with increases of 690% from 1995 to 2004 and 100% from 2004 to 2011. Over the same time period, opioid misuse increased more dramatically: 4,680% from 1996 to 2011, with increases of 1,372% from 1996 through 2004 and 245% from 2004 to 2011. The number of patients seeking treatment for opioid use disorder in this time period, not including heroin, increased 187%, whereas treatment-seeking increased 87% for heroin use disorder, 40% for marijuana use disorder, and decreased 7% for cocaine use

⁴⁷ Meldrum ML. *Opioids and Pain Relief: A Historical Perspective* (*Progress in Pain Research and Management*, V. 25). IASP Press; 2003, at pp. 195-199.

⁴⁸ Paulozzi LJ, Jones CM, Mack K a, Rudd R a. Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- {United States}, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(43):1487-1492, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm?s_cid=mm6043a4_w, at p. 1489.

disorder.⁴⁹ The increase in the medical use of opioid analgesics during this time period substantially contributed to increases in misuse and addictive use. The chart below, based on official government data, shows this close relationship⁵⁰:

**Rates of prescription painkiller sales and substance abuse treatment admissions
(1999-2010)**



SOURCES: National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 1999-2010; Treatment Episode Data Set, 1999-2009; Reproduced from Sullivan MD, *et al.*, Opioid therapy for chronic pain in the US. *Pain* 2013; 154:S94-100, Fig.2.

- ii. A study by Paulozzi *et al.*, published in 2006, analyzed death certificates from 1999-2002, and found that the most rapidly increasing category of death certificate-reported mortality was “opioid analgesic without heroin or cocaine,” which rose 129.2% in that time period, compared to deaths associated with heroin

⁴⁹ Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain Physician*. 2014, at p. E119.

⁵⁰ Centers for Disease Control and Prevention. *Prescription Painkiller Overdoses in the US infographic*. <https://www.cdc.gov/vitalsigns/painkilleroverdoses/infographic.html>, (last updated November 1, 2011).

alone (without prescription opioids or cocaine), which rose only 23.7%, and cocaine alone, which rose 16%.⁵¹ Paulozzi stated, “Overall, the relative increase in ARCOS opioid sales (76%) from 1999 to 2002 was consistent with the relative increase in opioid poisoning (95%).”⁵²

- iii. The Paulozzi article also reported a 73% increase in opioid-analgesia-related emergency department visits between 1999-2002.⁵³ Paulozzi *et al*’s conclusion is that prescription opioids alone were the principal cause of death during the early years of the opioid epidemic⁵⁴, with illicit drugs becoming more prevalent in later years, in part due to the higher cost and/or lesser availability of prescription opioids.
- iv. A June 4, 2020 report of the West Virginia Attorney General shows that prescription opioid-related deaths were the first and primary driver of opioid-related deaths in West Virginia from 2001-2015. The report notes, “heroin was associated with fewer than 70 overdose deaths a year until 2013, but (as shown in Table 1), hydrocodone and oxycodone crossed that threshold by 2007.”⁵⁵
- v. “By 2005, long-term opioid therapy was being prescribed to an estimated 10 million US adults. The volume of prescribed opioid analgesics was 100 MME [Morphine Milligram Equivalent] per person in 1997; in 2007, the MME per person had increased to almost 700 MME.”⁵⁶ By 2017, the level of MME had declined

⁵¹ Paulozzi LJ, *et. al.* Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiology and Drug Safety*. 2006;15:618-627, at p. 621.

⁵² *Id.*, at p. 624 See Appendix III to this Report, showing similar evidence for West Virginian and Cabell County.

⁵³ *Id.*

⁵⁴ *Id.*, at p. 626.

⁵⁵ State of West Virginia Office of the Attorney General, “DEA’s Failure to Combat Diversion Cost Lives: results from the West Virginia Attorney General’s Investigation into the DEA’s catastrophic failure to manage the National Drug Quota System from 2010-2016, (June 4, 2020), at p. 3.

⁵⁶ Paulozzi LJ, Weisler RH, Patkar A a. A national epidemic of unintentional prescription opioid overdose deaths: how physicians can help control it. *J Clin Psychiatry*. 2011;72(5):589-592. doi:10.4088/JCP.10com06560, at p. 589.

from its peak to 543.4 MME, which remains well over 5 times higher than the prescribing rate in 1997.⁵⁷

- vi. The number of long-term opioid users (daily for greater than 90 days) increased between 1999 and 2014. “Of all opioid users in 2013-2014, 79.4% were long-term users compared with 45.1% in 1999-2000.”⁵⁸ The increase in long-term use is important, because increased duration of use is also directly correlated with risk of addiction.⁵⁹
- vii. Between 2006 and 2015, 66% of patients receiving an opioid prescription in an ambulatory (outpatient) care setting had a diagnosis of non-cancer pain, and 28% had no pain diagnosis at all. Only 5% of patients had a cancer-related pain diagnosis. Absence of a pain diagnosis was more common in visits where an opioid prescription was continued (30.5%) than those in which an opioid was newly prescribed (22.7%).⁶⁰
- viii. As reported in an article I co-authored in 2016, more than one-third of Part D Medicare enrollees fill at least one opioid prescription in any given year. Part D covers 68% of the roughly 55 million people on Medicare.⁶¹ As such, more than 10 million Part D Medicare enrollees are exposed to a prescription opioid in any given year, thus becoming vulnerable to the adverse effects of opioids, including but not limited to addiction. Medicare represents just one patient population, suggesting that many millions of patient consumers in this country have been exposed to the risks of

⁵⁷ Schieber LZ, Guy, GP, Seth P, et al. Trends and Patterns of Geographic Variation in Opioid Prescribing Practices by State, United States, 2006-2017. *JAMA Netw Open*. 2019;2(3):e190665, at p. 1.

⁵⁸ Mojtabai R. National trends in long-term use of prescription opioids. *Pharmacoepidemiol Drug Saf*. 2017. doi:10.1002/pds.4278, at p. 526.

⁵⁹ Edlund MJ, Martin BC, Russo JE, Devries A, Braden JB, Sullivan MD. The Role of Opioid Prescription in Incident Opioid Abuse and Dependence Among Individuals With Chronic Noncancer Pain. *Clin J Pain*. 2014;30(7):557-564, at p. 557.

⁶⁰ Sherry TB, Sabety A, Maestas N. Documented Pain Diagnoses in Adults Prescribed Opioids: Results From the National Ambulatory Medical Care Survey, 2006–2015. *Ann Intern Med*. 2018;169(12):892-894, at p. 892.

⁶¹ Lembke et al., “Use of Opioid Agonist Therapy”, fn.7, above, at pp. 990-991.

prescription opioids in recent decades, both within and outside the Medicare-eligible populations.⁶²

- ix. In an evaluation of over one million Medicaid enrollees, one out of five pregnant women (21.6%) filled an opioid prescription. From 1992 to 2012, the proportion of pregnant women admitted to substance abuse treatment facilities that reported a history of prescription opioid addiction increased from 2% to 28%.⁶³
- c. As reported in another article I co-authored in 2016, increased opioid prescribing is distributed across different types of prescribers, relatively indifferent to individual physicians, specialty, or region.⁶⁴
 - i. In other words, opioid overprescribing is not merely the result of a small subset of so-called “pill mill” doctors, although such doctors do exist and have contributed to the current epidemic. Doctors across diverse medical specialties are prescribing more opioids.
 - ii. By specialty, pain doctors prescribe more opioids than doctors in any other specialties. However, by volume, family medicine and internal medicine doctors account for the most opioids, because there are more of them.⁶⁵
 - iii. But the salient finding was that the increase in opioid prescribing is not explained by a minority of prolific prescribers alone. Rather, opioid prescribing has increased broadly across a variety of specialties.⁶⁶
- d. A recent peer-reviewed publication evaluated prescriptions and diagnoses among enrollees in both commercial and Medicaid databases, and found that of 99,395 commercially insured and 60,492 Medicaid patients with an

⁶² A recent study by Romman is consistent with our own findings, *see e.g.* Romman AN, *et al.* Opioid Prescribing to Medicare Part D Enrollees, 2013-2017: shifting responsibility to pain management providers. *Pain Medicine*. 2020; 0(0): 1-9.

⁶³ Krans EE, Patrick SW. Opioid Use Disorder in Pregnancy: Health Policy and Practice in the Midst of an Epidemic. *Obstet Gynecol*. 2016 July; 128(1): 4–10, at p. 4.

⁶⁴ Chen et.al, “Distribution of Opioids”, fn.5, above, at p. 260.

⁶⁵ *Id.* at pp. 259-260.

⁶⁶ *Id.* at p. 260.

OUD diagnosis between 2005-2015, “most enrollees with OUD in the data had current opioid prescriptions.”⁶⁷ This supports the conclusion that prescription opioids are intertwined with opioid addiction, and that the paradigm shift in medicine toward liberal opioid prescribing has been a major factor contributing to the increased supply which has fueled this opioid epidemic.

- e. Although national average opioid prescribing has plateaued or decreased since its peak in 2012, there are still many cities, counties, and states across the nation where opioid prescribing continues to be high, and overall opioid prescribing in the US remains at levels far exceeding pre-1990 rates.
 - i. The U.S. national average number of opioid prescriptions written in 2012 was 81 opioid prescriptions per 100 persons (255 million total prescriptions). By 2016, the U.S. national average had decreased to 66 opioid prescriptions per 100 persons (214 million total). In 2017, the prescribing rate had fallen to its lowest in more than 10 years, at 59 prescriptions per 100 persons (total of more than 191 million total opioid prescriptions).⁶⁸
 - ii. However, prescribing rates in the United States are still greater than in the late 1990s, and greater than in other countries with comparable needs for analgesia. Further, in certain regions of the United States, opioid prescribing continues to remain very high, well above the national average. In 2017, according to the CDC, “In 16% of U.S. counties, enough opioid prescriptions were dispensed for every person to have one.” And “some counties had rates that were seven times higher than that.”⁶⁹

⁶⁷ Ali MM, et al., Opioid Use Disorder and Prescribed Opioid Regimens: Evidence from Commercial and Medicaid Claims, 2005-2015. *J Med Toxicol.* 2019 Jul;15(3):156-168. doi: 10.1007/s13181-019-00715-0. Epub 2019 May 31, at p. 156.

⁶⁸ Ctrs. for Disease Control and Prevention. *U.S. Opioid Prescribing Rate Maps.* <https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html>. See Appendix III to this Report, providing comparative, and substantially higher prescribing rates for West Virginia and Cabell County. In some years, the Cabell County prescribing rates were more than double the national average.

⁶⁹ *Id.*

- iii. Among 48 million individuals with any period of insurance coverage between January 2007 and December 2016, including commercial beneficiaries, Medicare Advantage beneficiaries aged 65 years and over, and Medicare Advantage beneficiaries under age 65 years (eligible owing to permanent disability), data show that prescription opioid use and average daily dose measured at the individual level have not substantially fallen from their peaks. “Across all years of the study, annual opioid use prevalence was 14% for commercial beneficiaries, 26% for aged Medicare beneficiaries, and 52% for disabled Medicare beneficiaries.”⁷⁰
- f. Opioid prescribing in the United States far exceeds that of other developed nations with aging populations and comparable population needs for pain relief.
 - i. Using International Narcotics Control Board figures, the United States consumed 173,332 kilograms of 574,693 kilograms of opioids consumed globally (382,131.6 of 1,266,981.2 pounds), or 30.2 percent.⁷¹
 - ii. Using “defined daily doses,” the United States consumed the most opioids per unit population from 2013 to 2015: 47,580 doses of narcotic drugs were consumed per day per million people. Canada comes in second with 34,444 defined doses consumed per million people per day, and Germany in third with 30,796; Japan was 50th at 1,223 defined doses/day.⁷²

4. The Pharmaceutical Opioid Industry contributed substantially to the paradigm shift in opioid prescribing through misleading messaging about the safety and efficacy of prescription opioids. The Industry disseminated these misleading messages through key opinion leaders, medical school curricula, continuing medical education courses, clinical decision support tools, professional medical societies, the Federation of State Medical Boards, and the Joint Commission.

⁷⁰ Jeffery MM, Hooten WM, Henk HJ, *et al.* Trends in opioid use in commercially insured and Medicare Advantage populations in 2007-16: retrospective cohort study. *BMJ*. 2018;362:k2833. doi:10.1136/bmj.k2833, at p. 1.

⁷¹ International Narcotics Control Board, Narcotic Drugs Technical Report 2016, at pp. 200-203. See https://www.incb.org/incb/en/narcotic-drugs/Technical_Reports/2016/narcotic-drugs-technical-report-2016.html.

⁷² *Id.* at pp. 226-228.

- a. The Pharmaceutical Opioid Industry targeted doctors and patients directly, by promoting key opinion leaders, by infiltrating continuing medical education courses, by supporting professional medical societies, and by co-opting medical watchdog organizations like the Federation of State Medical Boards and The Joint Commission, to convince prescribers and the broader health care system that liberal opioid prescribing is based on science, and that failing to prescribe opioids is tantamount to causing pain. They misrepresented marketing as education and used flawed and biased studies to achieve this goal. These misrepresentations were transmitted to medical students, residents, and early career physicians, leading to a paradigm shift in opioid prescribing, such that opioids became first-line treatment for minor and chronic pain conditions. In fact, there has never been sufficient evidence to justify widespread opioid prescribing. These actions directly contributed to the opioid epidemic we face today.⁷³
- b. Key opinion leaders
 - i. To encourage doctors to prescribe more opioids, opioid manufacturers promoted the careers of physicians who were sympathetic to their cause. They singled out vocal proponents of liberal opioid prescribing, especially for chronic pain conditions, and paid these physicians to promulgate the benefits and minimize the risks.⁷⁴
 - ii. These ‘key opinion leaders’ and others, including the Defendant manufacturers, actively promoted a 1980 *New England Journal of Medicine* Letter to the Editor by Porter and Jick, entitled

⁷³ As stated in a 2019 study, “The contribution of prescription opioids to the sharp rise in overdose deaths in the United States began in the late 1990’s and is primarily an iatrogenic problem, driven by an increase in opioid prescribing for persistent pain. The drivers of this increase are complex, including factors within the health care system (eg, adoption of the pain scale as the fifth vital sign, aligning physician incentive payments with patient satisfaction, pharmaceutical industry marketing) and public expectations for pain treatment.” Hedberg K, et al. Integrating public health and health care strategies to address the opioid epidemic: the Oregon Health Authority’s opioid initiative. *Journal of Public Health Management & Practice*. 2019;25(2):214-220, at p. 219 (emphasis added). As detailed in this section of the Report, the Pharmaceutical Opioid Industry promoted the “drivers” referenced in the quoted text, including the “fifth vital sign” and “patient satisfaction” based on pain scores.

⁷⁴ Saper JR. The Influence of Pharma and Device Manufacturers on APS and other PMAs: A War Within a War. (MDL No. 2804 Saper Dep. Ex. 6, at pp. 3-4).

“Addiction Rare in Patients Treated with Narcotics.”⁷⁵ Porter and Jick described that among hospitalized patients taking opioids for pain, they found only four cases of addiction among 11,882 patients treated with opioids. This letter was used as evidence by Defendants and key opinion leaders to argue that opioid addiction is rare in the course of medical treatment, despite the fact that the so-called evidence was of poor quality and not representative of patients seen in usual clinical care. The catch phrase “less than 1% get addicted,” based on this one data point, was used in opioid manufacturers’ branded advertisements and other promotional materials. (See Appendix I on promotional material.)

- iii. Significantly, the population in question in the Porter and Jick article is described as “hospitalized,” and receiving at least one dose of an opioid, without any reference to the size of the dose or range of duration of exposure. There is no reasonable basis to compare the risk of addiction among hospitalized patients who may have received only a single dose or short term course of opioid medication, with the far greater risk among patients prescribed opioids for non-cancer chronic pain, outside the hospital setting. This is especially true in light of the well-known relationship between longer duration of opioid exposure and increased risk of dependence and abuse. Despite the lack of reasonable or scientific basis for using Porter and Jick to support the concept of the “rarity” of addiction, Defendants and their key opinion leaders frequently cited this letter to the editor as if it provided sound scientific support for wide prescribing of opioids. (See Appendix I on promotional material.)
 - A. A 2017 study reported in the New England Journal of Medicine found that the Porter and Jick letter had been cited 608 times, compared to a median of 11 citations to other letters published contemporaneously. The authors stated: “In conclusion, we found that a five-sentence letter published in the Journal in 1980 was heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy. We believe that this citation

⁷⁵ Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med.* 1980;302(2):123.

pattern contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers' concerns about the risk of addiction associated with long-term opioid therapy. In 2007, the manufacturer of OxyContin and three senior executives pleaded guilty to federal criminal charges that they misled regulators, doctors, and patients about the risk of addiction associated with the drug. Our findings highlight the potential consequences of inaccurate citation and underscore the need for diligence when citing previously published studies.”⁷⁶

- B. The following are examples of Pharmaceutical Opioid Industry-sponsored, inappropriate and misleading reliance upon the Porter and Jick letter: (i) In 1996, a Purdue Frederick-funded study reported that: “In three studies involving almost 25,000 patients without a history of drug dependence, there were only 7 cases of iatrogenic addiction.”⁷⁷ (Citing Porter and Jick and 2 other inapplicable studies by Perry and Medina, discussed in this Report at §4.b.viii -ix, below). Moulin *et al.* described the risk of addiction as “negligible.”⁷⁸ Purdue Frederick is listed as a grant supporter of the Moulin article.⁷⁹ (ii) In 1997, Purdue published “I Got My Life Back” a brochure and video promoting a “*less than 1%*” addiction rate, citing to Porter and Jick (1980);⁸⁰ (iii) In 1998, a Janssen-funded study reported that a “*low risk* of iatrogenic psychological dependence has been observed in patients without a history of substance abuse” citing to Porter and Jick (1980);⁸¹ (iv) A 2001 Janssen presentation, “Optimizing Chronic Pain Management with Duragesic,” cites Porter and Jick (1980)

⁷⁶ Leung PTM, *et al.* A 1980 Letter on the Risk of Opioid Addiction. *N Engl J Med.* 2017; 376:2194-2195, at p. 2194

⁷⁷ Moulin DE et al. Randomised trial of oral morphine for chronic non-cancer pain. *Lancet.* 1996;347:143-147, at p. 143.

⁷⁸ *Id.*, at p. 147.

⁷⁹ *Id.*

⁸⁰ PKY183063227 (brochure); PPLPC009000022561 (video transcript) (emphasis added)

⁸¹ Dellemijn PLI, *et. al.* Prolonged treatment with transdermal fentanyl in neuropathic pain. *Journal of Pain and Symptom Management.* 1998;16(4):220-229, at pp. 227-228. (emphasis added)

for “low” risk of addiction in non-addicts and states that “the potential for addiction is in the patient, not the opioid.”;⁸² (v) In 2001, an Endo-sponsored KOL (Dr. Covington, Cleveland Clinic) presentation and handout titled “Opioid maintenance in chronic non-malignant pain” concluded that “Iatrogenic addiction in treatment of acute pain is *virtually nonexistent*” citing to Porter and Jick (1980);⁸³ (vi) In 2002, a Cephalon annual sales meeting presentation entitled, “The Myth of Addiction” concluded there was a “*0.06% chance of becoming addicted*” citing to Porter and Jick,⁸⁴ and directed its sales force: “Never Refer to Addiction when talking about opioids – especially Actiq!”⁸⁵ These examples demonstrate the point made in the 2017 *NEJM* article, that the Porter and Jick Letter was “heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy,” and “contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers’ concerns about the risk of addiction associated with long-term opioid therapy.”⁸⁶

- iv. An article by Portenoy 1986 co-author Foley and others stated, “We disagree with the concept of setting a maximum dose. The pharmacology of opioid use in the treatment of pain is based on dose titration to effect.”⁸⁷ This statement encouraged the practice of increasing the dose of opioids over time as tolerance developed. I have seen scores of patients over the years on very high doses of opioids, some as high as 2,000 morphine milligram equivalents per day (MED), putting them at high risk for opioid-related morbidity and mortality. Meanwhile, there is no reliable evidence to support the use of higher doses of opioids, and mounting evidence that risks of opioids are directly related to dose and duration: the higher the dose, and the longer patients are on them, the higher the risk.

⁸² JAN-MS-00653403 (December 14, 2001), at *66 (produced natively).

⁸³ ENDO-OPIOID_MDL-02002494; ENDO-OPIOID_MDL-02002495 at slides 4-5 (emphasis added)

⁸⁴ TEVA_AAMD_00791885 at 1901-1902 (emphasis added)

⁸⁵ TEVA_AAMD_00791885 at 1887

⁸⁶ Leung, “A 1980 Letter”, fn. 76, above, at p. 2194.

⁸⁷ Foley KM, Fins JJ, Inturrisi CE. A true believer’s flawed analysis. *Arch Intern Med.* 2011. doi:10.1001/archinternmed.2011.166, at p. 867.

- v. Edlund *et al.* state, “Clinicians should be aware that as they proceed from acute to chronic opioid therapy, the evidence of efficacy decreases whereas the opioid use disorder (OUD) risk increases substantially.”⁸⁸ The odds of developing an OUD in those exposed to opioids for 90 days or more, compared to those not exposed (odds ratio), are as follows: For low dose (1-36 MMEs per day), the odds ratio was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) the odds ratio was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) the odds ratio was 122.45 (95% CI = 72.79, 205.99).⁸⁹ Another way to say this is that patients exposed to 120 MMEs of opioids for 90 days or more, were 122 times more likely to develop an opioid use disorder within the year than those not exposed to opioids.
- vi. These data from the Edlund study show that both dose and duration affect the risk of opioid use disorder. That is, the higher the dose, the greater the risk; and the longer the duration of exposure, the greater the risk. When both higher dose and longer duration are found, patients are 120 times more likely to suffer from opioid use disorder than patients who were not prescribed opioids.
- vii. Other articles cited by key opinion leaders and Defendants on low addiction rates in pain patient populations, included a national survey of burn facility staff with knowledge of >10,000 burn patients administered opioids, with no cases of iatrogenic addiction identified.⁹⁰ Burn debridement, consisting of the removal of dead tissue to promote healing, is a procedure carried out in a hospital setting. Mean administered morphine during the procedure was only 8.9 mg, a very low dose. Although the authors referred to continued narcotic therapy after debridement, no details were provided regarding dose or duration, and burn healing is inherently

⁸⁸ Edlund, *et al.*, Role of Opioid Prescription,” fn.59, above, at p. 561,

⁸⁹ *Id.* at p. 559-60. As shown in Table 3 at p.561, based on Edlund’s data, the OR with increasing dose and duration is far greater than the OR for other factors, such as prior substance use disorders or psychiatric diagnoses.

⁹⁰ Perry, S, Heidrich, G, Management of pain during debridement: A survey of U.S. burn units. *Pain*. 1982;13(3):267-280, at. 267-77.

<http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=eemed1a&NEWS=N&AN=1982178505>.

a time-limited process unlike chronic arthritis, back pain, or other conditions for which Defendants promoted opioid therapy. As in the case of the Porter and Jick letter, the low risk of addiction for a short-term, hospital-based procedure and its limited sequelae are not comparable to the significant risk of addiction with long-term opioid therapy for chronic pain, and it is misleading to cite the burn study to support a claim of low addiction risk of opioids. Further, the study was not *a priori* designed to study addiction outcomes and did not use rigorous methodology to study this outcome.

- viii. Defendants and their key opinion leaders also cited a survey study of a large headache clinic by Medina, *et al.*, in support of the claim that risk of addiction was low.⁹¹ Sixty-two patients fulfilled criteria for inclusion in the study, in that they had been prescribed either a narcotic (codeine or propoxyphene), or a barbiturate (butalbital) or both. Thirty-eight of the 62 patients were treated with butalbital, a Schedule III medication in the class of barbiturates, and six were treated with propoxyphene (Darvon), a Class IV drug. The authors reported, “Eight were dependent; six physically addicted, two psychologically dependent and two were abusers There is danger of dependency and abuse in patients with chronic headaches.” Reliance upon the Medina study to suggest absence of risk appears to contradict the interpretation of the data by the authors themselves, who explicitly acknowledged the dangers. The authors also used conflated definitions of dependence, addiction, and ‘abuse’ not consistent with other studies or with DSM criteria of any edition; however, the finding that two patients were “psychologically dependent” would generally have been considered equivalent to a diagnosis of “addiction” at the time of the Medina article. In addition, the study did not use objective criteria for tracking misuse, such as urine toxicology or collateral information from family or the prescription drug monitoring database, which would have increased the investigators’ likelihood of identifying aberrant behavior.

⁹¹ Medina JL, Diamond S. Drug Dependency in Patients with Chronic Headaches. *Headache J Head Face Pain*. 1977;17(1):12-14. doi:10.1111/j.1526-4610.1977.hed1701012.x, at pp. 1-2.

- ix. Key opinion leader Dr. Russell Portenoy, former chairman of the Department of Pain Medicine and Palliative Care at Beth Israel Medical Center in New York City, conceded in 2011 that there was no reliable evidence to support the statement that opioids are ‘low risk.’ In a taped interview with Dr. Portenoy in 2011, Portenoy described his promotion of opioids in the 1990s and early 2000s: “I gave so many lectures to primary care audiences in which the Porter and Jick article⁹² was just one piece of data that I would then cite. I would cite 6 to 7 maybe 10 different avenues of thought or evidence, *none of which represents real evidence*. And yet what I was trying to do was to create a narrative so that the primary care audience would look at this information *in toto* and feel more comfortable about opioids in a way they hadn’t before. . . . Because the primary goal was to de-stigmatize, *we often left evidence behind.*⁹³”⁹³ (emphasis added). Dr. Portenoy’s statement supports my opinion that there was no reliable evidence that opioids are low risk.

- x. Between 1997 and 2012, Dr. Portenoy received nearly \$29,000 in direct payments from Janssen and its parent Johnson & Johnson (J&J), including \$16,940 for “sponsored research”.⁹⁴ Dr. Portenoy spread his pro-opioid messages as President of the American Pain Society, and as a member of the boards of the American Pain Foundation and the American Pain Society, organizations that received funding from the Pharmaceutical Opioid Industry.⁹⁵ The many hundreds of thousands of dollars in Pharmaceutical Opioid Industry payments to individuals such as Dr. Portenoy are further evidence of Industry support for “key opinion leaders” whose work

⁹² Porter, Jick, *et al.*, “Addiction Rare,” fn. 75, above.

⁹³ Lurie J., *Doctors Receive Opioid Training. Big Pharma Funds It. What Could Go Wrong?* Mother Jones. <https://www.motherjones.com/politics/2018/04/doctors-are-required-to-receive-opioid-training-big-pharma-funds-it-what-could-go-wrong/>.

⁹⁴ JAN-MS-00000001 at 0008.

⁹⁵ Declaration of Russell K. Portenoy, M.D. in MDL 2804, at ¶ 37-40.

was used by the Industry to encourage opioid prescribing through aggressive misrepresentation of risks and benefits.⁹⁶

- xii. In a 2001 discussion regarding abuse reports relating to Duragesic, Janssen's VP of Pain, Steve Zollo stated, "let's be clear about this issue – As the use of Duragesic continues to rise (which it will), so will drug abusers trying to find creative ways to extract fentanyl from the patch. That's why it's a scheduled drug. As our use goes up, so will published reports of abuse."⁹⁷
- xiii. Yet in a 2001 Duragesic patient guide, Janssen made false and misleading statements regarding the addiction potential of Duragesic, stating that "addiction is relatively rare when patients take opioids appropriately."⁹⁸

c. Medical School Curricula

- i. In 2003, Purdue entered into an agreement with Harvard Medical School that provided for a significant financial contribution from Purdue to Harvard, as well as a cooperative arrangement between the two entities in developing curriculum and materials for instruction about pain management. In particular, Attachment B to the Agreement provides that (i) "Purdue Pharma shall be encouraged to suggest ideas for areas where education in the field of pain is needed, and for curriculum which might meet such needs"; (ii) "Purdue Pharma shall be encouraged to suggest ideas for CME [Continuing Medical Education] courses"; and (iii) with respect to the goals of the educational program, "Purdue Pharma shall be encouraged to make suggestions concerning such courses and materials."

⁹⁶ Senate Homeland Security and Gov Affairs Comm, 116th Cong., Report on Fueling an Epidemic Report Two: Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups (2018) at pp. 10-11, <https://www.hsgac.senate.gov/imo/media/doc/REPORT-Fueling%20an%20Epidemic-Exposing%20the%20Financial%20Ties%20Between%20Opioid%20Manufacturers%20and%20Third%20Party%20Advocacy%20Groups.pdf>.

⁹⁷ JAN-MS-00287030 at 7031.

⁹⁸ JAN-MS-02757826 at 7847.

- ii. I also personally experienced the influence of the pharmaceutical industry on the curriculum during my own medical education in the 1990s.
- d. Continuing Medical Education.
 - i. The practicing physician relies on continuing medical education (CME) conferences to acquire state of the art knowledge about the latest scientific evidence in medical practice. The average clinician busy seeing patients cannot wade through the voluminous literature him or herself. Instead, (s)he attends CME conferences, and assumes that the knowledge disseminated there, especially by esteemed academic colleagues, represents unbiased research. The FDA hires independent auditors to review CME courses to make sure they're following a blueprint and are free of pharmaceutical influence, but auditors are required to audit no more than 10% of all CME.⁹⁹ (See discussion of one example of an opioid CME designed by Mallinckrodt, in Appendix I)
 - ii. Drug company-sponsored continuing medical education (CME) preferentially highlights the sponsor's drug(s) compared with other CME programs. The average physician attending CME courses underestimates the influence of industry-sponsored speakers and industry-sponsored CME, which is considerable. Data show changes in prescriber practice in favor of the sponsor's drug, after participation in an industry sponsored CME event.¹⁰⁰
 - iii. Not only has drug-company involvement in continuing medical education programs become prolific generally over the past several decades, but Defendants employed CME as part of the strategy to deploy their message about opioids starting in the late 1990s and continuing to today.¹⁰¹

⁹⁹ Lurie, "Doctors Receive Opioid Training", fn. 93, above, at p. 3.

¹⁰⁰ Wazana A. Physicians and the pharmaceutical industry: Is a gift ever just a gift? *JAMA*. 2000;283(3):373-380. <http://dx.doi.org/10.1001/jama.283.3.373>, at pp. 373, 377-78.

¹⁰¹ Saper, "The Influence of Pharma," fn. 74, above, at p. 2.

- iv. The use of “Speakers Bureaus” of doctors, trained by a drug company to promote its product, is an adjunct to the CME strategy. “From 1996 to 2001, Purdue conducted more than 40 national pain-management and speaker-training conferences at resorts in Florida, Arizona and California. More than 5000 physicians, pharmacists, and nurses attended these all-expenses paid symposia, where they were recruited and trained for Purdue’s national speaker bureau. It is well-documented that this type of pharmaceutical company symposium influences physicians’ prescribing, even though the physicians who attend such symposia believe that such enticements do not alter their prescribing patterns.”¹⁰²
- v. Teva/Cephalon Pharmaceutical’s “2005 ACTIQ Marketing Plan” tactical summary of sales strategies clearly delineate how they planned to use misleading marketing messages in the form of “continuing medical education” to promote their products, including their branded-fentanyl product “Actiq.” As explained in Appendix 1B of this Report, Teva/Cephalon’s strategy focused on persuading doctors of the need for ACTIQ as a supplement to chronic opioid therapy, to treat so-called “Breakthrough Pain,” (BTP) when in fact such patients likely sought greater doses of opioids because they had experienced “tolerance,” that is, they needed greater amounts of opioids to get the same degree of pain relief. See excerpted quotes below which describe Teva/Cephalon’s CME plan:
 - A. “ACTIQ marketing strategies will be executed through a variety of tactical initiatives that convey ACTIQ key messages and differentiate ACTIQ from its competitors based on its primary patient benefit, rapid onset of analgesia and pain relief.... Both promotional and continuing medical education programs will be implemented in 2005 and will continue to comprise a critical component of the tactical plan. New in 2005 is *Emerging Solutions in Pain (ESP)* which is an initiative developed by physicians for physicians, pharmacists and

¹⁰² Van Zee A. The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. *Am J Public Health*. 2009. doi:10.2105/AJPH.2007.131714, at pp.221-22.

other healthcare professionals, to address some of the most critical issues in pain management today.”¹⁰³

- B. “Continuing Medical Education CME played a vital role in the education of physicians, nurses and pharmacists in 2004 regarding chronic cancer pain and non-cancer pain and Abuse, Addiction and Diversion. The major CME initiatives in 2004 included a CME on-demand teleconference, local and regional CME symposia (CEP Lectures), a tri-mesterly newsletter entitled Emerging Solutions in Pain, a repository website by the same name EmergingSolutionsinPain.com, sponsorship of the Pharmacologic Management of Pain Resource Center on Medscape and the sponsorship of the Breakthrough Cancer Pain category on pain.com, the most popular pain website on the internet. Additional CME initiatives included a CME insert in CME-TODAY for Primary Care Physicians and CME Symposia at the annual congresses for AAPM, AAPM&R and the Northeast PRJ-MED .”¹⁰⁴
- C. “The local and regional CME Symposia represented one of the most significant educational efforts in the area of pain management in 2004. These symposia allowed for the scientific exchange of extensive information on diagnosis, assessment and management of various pain related issues. Approximately 214 of these programs are expected to be completed by year end.”¹⁰⁵
- D. “The tri-annual newsletter, Emerging Solutions in Pain, currently has a circulation of over 11,000 clinicians (8,000+ physicians and 2000+ nurses). The newsletter allows for communication of information on diagnosis and management of various pain types, in two distinct media:

¹⁰³ TEVA_CAOC_00759630 at 9634.

¹⁰⁴ *Id.* at 9664.

¹⁰⁵ *Id.*

written and CD-ROM. The accompanying website serves as a repository for all CME programs created.”¹⁰⁶

- vi. I have personally experienced this strategy of marketing messages misrepresented as CME. For example, in 2001, every licensed physician in the state of California was mandated to attend a day-long CME course on the treatment of pain as a requirement to maintain licensure. I attended that day-long course, in which use of opioids was promoted. I recall that there was no accurate presentation of the risks of opioids, and the messages that were provided tracked the misconceptions described above regarding overstatement of the benefits of opioids.

e. Clinical Decision Support Tools

- i. Clinical decision support (“CDS”) tools help doctors know when and how to provide certain types of treatments. They provide nudges based on flowcharts and algorithms, which are presumably based on hard science. They come in many different forms, from reminders on pocket cards, to infographics on wall posters, to prompts and alerts in the electronic medical record system.¹⁰⁷ If these tools are corrupted by commercial influence, they provide a very dangerous and insidious form of corruption because they are invisible to the consumer.
- ii. For example, in January 2020, Practice Fusion, Inc, a provider of electronic health records (EHRs) including CDS tools embedded within the EHRs, “admitted to conspiring with an opioid manufacturer to create a pain alert tool to encourage physicians to prescribe more extended release opioids,” and agreed to pay \$145 million to resolve criminal and civil allegations that it accepted ‘kickbacks’ in exchange for creating and implementing a CDS that promoted such prescribing.¹⁰⁸

¹⁰⁶ *Id.*

¹⁰⁷ U.S. Department of Health and Human Services. *Clinical Decision Support*. (April 10, 2018).

<https://www.healthit.gov/topic/safety/clinical-decision-support>

¹⁰⁸ Taitsman JK, et. al. Commercial Influences on Electronic Health Records and Adverse Effects on Clinical Decision Making. *JAMA Intern Med*. 2020;10.1001/jamainternmed.2020.1318. doi:10.1001/jamainternmed.2020.1318, at p. E1.

iii. According to an article in *JAMA*, “The resulting alerts promoted opioid prescribing that deviated from accepted medical standards by suggesting extended-release opioids as a treatment option for patients with less than severe pain, even if nonopioid or immediate-release opioid alternatives could have adequately controlled the pain. Physicians who received these pain alerts prescribed extended-release opioids at a higher rate than those who did not.”¹⁰⁹ A statement by the United States Department of Justice stated, “In marketing the ‘pain’ CDS alert, Practice Fusion touted that it would result in a favorable return on investment for the opioid company based on doctors prescribing more opioids.”¹¹⁰ Such prescribing exposed patients to increased risks of harms caused by prescription opioids.

f. Professional Medical Societies

- i. According to Janssen’s response to a May 2012 US Senate Finance Committee request, between 1997-2012 Janssen and its parent J&J made payments to professional societies that advocated unwarranted expanded use of opioids, under the guise of practice guidelines, including the American Pain Society, the American Academy of Pain Medicine, Joint Commission Resources and others totaling more than \$4 million dollars.¹¹¹ From 2012-2017, Janssen continued payments and close coordination with these groups, providing almost a half a million dollars in funding. Janssen also acknowledged making payments via a third party to front groups including the American Pain Society and American Academy of Pain Medicine.¹¹²
- ii. Joel Saper, M.D., a past board member of the American Pain Society (APS), testified that the American Pain Society (APS)

¹⁰⁹ *Id.*

¹¹⁰ US Department of Justice. *Electronic Health Records Vendor to Pay \$145 Million to Resolve Criminal and Civil Investigations* (January 27, 2020). <https://www.justice.gov/opa/pr/electronic-health-records-vendor-pay-145-million-resolve-criminal-and-civil-investigations-0>

¹¹¹ JAN-MS-00000001.

¹¹² HSGAC Report, “Fueling an Epidemic”, fn. 96, above, at pp. 1, 17.

received financial support from the Pharmaceutical Opioid Industry, which he referred to as “narcopharma.”¹¹³

- iii. Consistent with and supportive of my personal experience, Dr. Joel Saper testified that “the educational programs of AAPM [American Academy of Pain Management] and APS particularly as they involve opioid advocacy, were greatly influenced by commercial largess. In my opinion, commercial dynamics influenced, if not steered, the selection of abstracts, course topics, and faculty to commercially friendly participants as it involved opioid advocacy, largely ignoring those imposing or exhorting caution against the growing advocacy for opioids for chronic nonmalignant pain.”¹¹⁴
- iv. Dr. Saper testified that such educational programs of AAPM and APS involving opioid advocacy were “inappropriate”,¹¹⁵ and I agree.
- v. Dr. Saper further stated that “APS and AAPM and its members have participated, if not promoted, this crisis by failing to assure the presentation of unbiased, balanced educational programs and guideline development, thereby protecting the public from commercial influence through undisclosed support from the Pharmaceutical Opioid Industry. In failing to do so, the organizations failed to protect patients.”¹¹⁶
- vi. In 2009, Janssen partnered with the American Geriatrics Society and American Academy of Pain Medicine to create a 2009 patient education guide entitled, “Finding Relief: Pain Management for

¹¹³ Saper JR. The Influence of Pharma and Device Manufacturers on APS and other PMAs: A War Within a War. (MDL No. 2804 Saper Dep. Ex. 6, at p. 5).

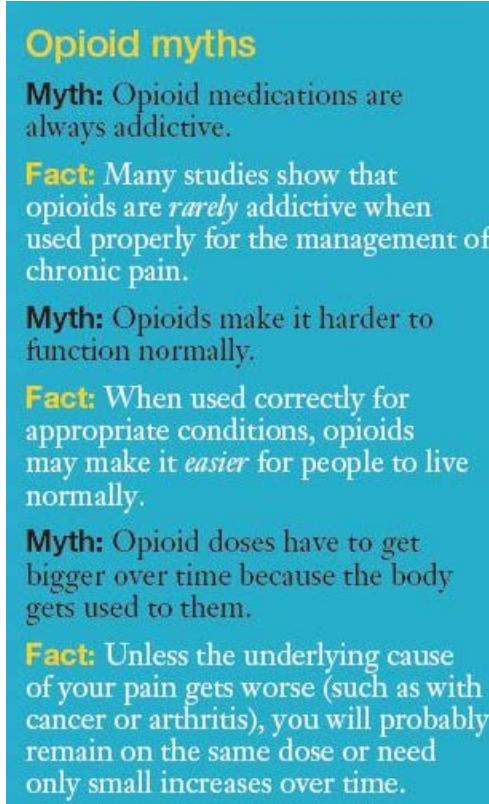
¹¹⁴ Deposition of Joel R. Saper, M.D., January 11, 2019, MDL No. 2804, at 92:13-22.

¹¹⁵ *Id.* at 93:15-19.

¹¹⁶ *Id.* at 115:24-116:6.

Older Adults.”¹¹⁷ In 2010, Janssen paid the American Geriatrics Society more than \$158,209 for “educational grants.”¹¹⁸

- vii. The “Finding Relief” patients’ guide included the claims shown below.¹¹⁹ These claims were false and misleading in that addiction to prescription opioids is common, not rare, and chronic use does not confer substantial benefit, as discussed later in this Report.



- viii. Further, an internal Purdue Pharma email from Richard Sackler to Paul Goldenheim, dated April 13, 2001, concerned a planned meeting with “leaders of APS, APF [American Pain Foundation] and other pain societies.” Dr. Sackler stated, “Our goal is to bind

¹¹⁷ HSGAC Report, “Fueling an Epidemic”, fn.96, above, at p. 13.

¹¹⁸ JAN-MS-00000001 at 0007.

¹¹⁹ JAN-MS-00000306 at 0315.

these organizations more closely to us than heretofore, but also to align them with our expanded mission and to see that the fate of our product(s) are [sic] inextricably bound up with the trajectory of the pain movement.”¹²⁰

- ix. These documents and testimony support my opinion that the Pharmaceutical Opioid Industry improperly supported the pro-opioid mis-education of medical professionals in order to increase sales of prescription opioids that resulted in an unprecedented epidemic of drug-induced mortality and morbidity. As I have written and stated elsewhere, doctors must bear some responsibility for the over-prescribing of opioids for chronic pain. However, the Pharmaceutical Opioid Industry bears the far greater share of the responsibility, for its role in promoting false messages of substantial benefit and low risk of opioids that influenced doctors to prescribe.

g. The Federation of State Medical Boards

- i. The Federation of State Medical Boards (FSMB) is a national organization that oversees the 70 medical and osteopathic boards of the United States and its territories. The State Board organizations serve many functions, but the most important is to exert disciplinary action against doctors who are deemed dangerous to patients. One of the most severe forms of disciplinary action is to revoke a doctor’s license to practice medicine.
- ii. In 1998, the Federation of State Medical Boards released a policy to reassure doctors that they would not be prosecuted if they prescribed even large amounts of opioids, as long as it was for the treatment of pain. Further, the Federation urged state medical boards to punish doctors for under-treating pain. Doctors lived in fear of disciplinary action from the State Medical Boards and the lawsuit that usually followed, if they denied a patient opioid painkillers.
- iii. The Federation of State Medical Boards published a book promoting the use of opioid painkillers. This book was sponsored

¹²⁰ PPLPC045000004928 at 4929

by a “consortium” that included Abbott Laboratories, Alpharma Pharmaceuticals, Cephalon, Inc., Endo Pharmaceuticals, and the Wisconsin PPSG.¹²¹ (See Appendix II.)

- iv. As detailed in Appendix II to this Report, the Pharmaceutical Opioid Industry provided substantial funding to the Wisconsin PPSG, which lobbied State Medical Boards to increase access to opioids, preclude punishment if opioids were prescribed for pain, and classify undertreatment of pain as inappropriate conduct. PPSG played a central role in revising the Federation of State Medical Board’s Model Guidelines on the Use of Controlled Substances for Pain Management¹²², now entitled Model Policy for the Use of Controlled Substances for Pain Management.¹²³
- v. The American Pain Society, funded and influenced by the Pharmaceutical Opioid Industry, supported University of Wisconsin Pain and Policy Study Group (PPSG) professors David Joranson and June Dahl to “visit boards of medicine in state after state to argue the importance of lessening the regulation of doctors who prescribe opioids for cancer, acute, and end-of-life pain.”¹²⁴ In 1995, APS created a Regulatory Issues Committee and a Public Affairs Committee, with Joranson in a leadership role of both these Committees.¹²⁵ James Campbell, then President of APS, stated that “myths of liability for addiction” and “fear of government regulation” caused “underuse” of opioids for chronic pain.¹²⁶ These Committees had a mission to persuade State legislatures to ease restrictions on opioid prescribing, and to protect doctors from discipline for prescribing them. [Campbell asserted, “We need to train doctors and nurses to treat pain as a

¹²¹ Fishman, S.(ed.), “Responsible Opioid Prescribing: A Physician’s Guide” (Federation of State Medical Boards, Waterford Life Sciences, 2007).

¹²² WIS_PPSG_008292.

¹²³ Federation of State Medical Board’s Model Guidelines on the Use of Controlled Substances for Pain Management (2004), http://www.fsmb.org/Policy%20Documents%20and%20White%20Papers/2004_model_pain_policy.asp

¹²⁴ Saper, “The Influence of Pharma,” fn. 74, above, at p. 9.

¹²⁵ Campbell 1995; APS Presidential Address; Pain Forum 1996; 85-88, at p. 87.

¹²⁶ *Id.*

vital sign,” that hospitals’ standard of care should include measures of the facilities’ efforts to treat pain.¹²⁷ APS explicitly stated that it would seek “backing from industry,” along with the public and its members, for a pain “foundation,” to further its messages.¹²⁸ These industry-funded efforts contributed significantly to the paradigm shift in opioid prescribing that gave rise to the opioid epidemic.

- vi. In addition to the indirect support by the Industry through the APS, direct financial support to PPSG was provided by the Pharmaceutical Opioid Industry, as revealed in documents produced by PPSG and summarized in Appendix II to this Report. Those documents show substantial contributions by several opioid manufacturers, including Janssen, Endo, Ortho-McNeil (an affiliate of Johnson and Johnson), Alpharma,¹²⁹ and Cephalon, over a period of over a decade, during which PPSG justified its recurring requests for further funding on the basis of its successful efforts to loosen restrictions on opioid prescribing by lobbying State Medical Boards, presentations at professional conferences, leading industry-friendly Continuing Medical Education seminars, and publications in the scientific literature. (*See* Appendix II to this Report).
- vii. The Pharmaceutical Opioid Industry and PPSG influenced states to adopt intractable pain laws that encouraged opioid prescribing by shielding physicians from liability. Although the statutes may have initially been intended for cancer, acute, and end-of-life pain, the statutes do not necessarily include any such limitations, and the West Virginia statute did not restrict its protective shield to those circumstances.¹³⁰ Intractable pain laws in various states, including

¹²⁷ *Id.* at pp.86-87

¹²⁸ *Id.* at p.87.

¹²⁹ Actavis (now Allergan) acquired Kadian from Alpharma in 2008; *see* Press Release, Actavis, Actavis Acquires Kadian; Extends Specialty Drug Portfolio in U.S., (Dec. 30, 2008), <https://www.businesswire.com/news/home/20081230005227/en/Actavis-Acquires-Kadian-Extends-Specialty-Drug-Portfolio>.

¹³⁰ WV Code § 30-3A-2 (1998), Limitation on disciplinary sanctions or criminal punishment related to management of intractable pain, http://www.wvlegislature.gov/Bill_Text_HTML/1998_SESSONS/RS/Bills/HB4058%20ENR.htm. Code was updated in 2012 to remove reference to exceeding average dosage. See WV Code § 30-3A-2 (2012), Limitation on

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West Virginia, opened the floodgates to physicians' prescribing more opioids, while insulating them from disciplinary action.. In particular, under the West Virginia Management of Intractable Pain Act of 1998, a physician was not subject to either disciplinary sanctions or criminal punishment for administering or dispensing pain-relieving controlled substances, even when the dosage exceeded the average dosage of a pain-relieving controlled substance.¹³¹ J&J and Janssen worked with the Robert Wood Johnson Foundation ("RWJF"), which paid \$5,926,294.00 in grants to the University of Wisconsin-Madison School of Medicine, the eventual home of the PPSG between 1997 and 2004.¹³² Dr. Richard Payne (co-chair of the National Pain Education Council (NPEC) with Russell Portenoy) was on the Janssen and RWJF medical advisory boards during overlapping periods.¹³³ NPEC was a Janssen-funded front group which Janssen launched in support of the Duragesic tactical plan.¹³⁴ RWJF also funded the creation and dissemination of the Model State Guidelines through the Federation of State Medical Boards and its collaboration with PPSG, and provided funding to The Joint Commission as well.¹³⁵

- viii. According to PPSG's ranking system, West Virginia received a Grade of "C" in 2000; the Grade was "improved" to "B" in 2003 and 2006; and ultimately "improved," to a "B+" in 2012.¹³⁶ According to PPSG, West Virginia and six other states "improved" their grade by repealing statutes that either mandated alternative

Footnote continued from previous page

disciplinary sanctions or criminal punishment related to management of pain,
<http://www.wvlegislature.gov/wvcode/Code.cfm?chap=30&art=3A>.

¹³¹ *Id.*

¹³² MDL_RWJF_0000001: Grant ID 032037 for \$1,601,991; MDL_RWJF_0000003: Grant ID 036509 for \$998,000; MDL_RWJF_0000004: Grant ID 036547 for \$998,865; MDL_RWJF_0000005: Grant ID 037589 for \$1,408,628; MDL_RWJF_0000009: Grant ID 043412 for \$200,450; MDL_RWJF_0000010: Grant ID 043940 for \$421,800; MDL_RWJF_0000012: Grant ID 048204 for \$183,680; MDL_RWJF_0000013: Grant ID 051813 for \$112,880.

¹³³ JAN-MS-00402671.

¹³⁴ JAN-MS-00306713.

¹³⁵ PDD1706042217.

¹³⁶ PPLPC01700046138 at 6152; PPLPC017000514276 at 4282.

treatment before use of opioids, or stated or implied that opioids were a treatment of “last resort.”¹³⁷ These so-called “improvements” encouraged improper use of opioids, and the more recent Guidelines of the CDC and others have reversed the PPSG’s industry-funded accomplishments by encouraging the use of alternative treatments before opioids are employed. For example, the West Virginia “Best Practices Toolkit,” adopted in 2016, states, “One of our goals with these guidelines is to dramatically reduce the use of opioids as a first-line treatment option for patients with pain and *significantly increase the use of non-opioid alternatives for these patients*,” and further advises doctors to “[i]mplement a tiered approach for prescribing opioids for pain and *take every possible step to utilize non-opioid options first*.¹³⁸

- ix. Despite the absence of reliable evidence for the use of long-term opioid therapy in the treatment of chronic pain, the Pharmaceutical Opioid Industry sought to shame prescribers into opioid prescribing, by claiming that the ‘failure’ to prescribe opioids was tantamount to causing pain, and to scare them into prescribing by suggesting reprisal from regulatory bodies like The Federation. In their promotional material and “Train the Trainer” course, Defendants frequently invoked sources that characterized opioid prescribing as a moral obligation, and the failure to prescribe as the equivalent of causing pain, leading to legal sanctions. (*See Appendix I for more detail*)
- x. I remember that fear of ‘undertreating pain’ permeated medical practice and culture at this time. Doctors in some states were subject to the risks of disciplinary action from the board, and lawsuits that could follow, if they denied a patient’s request for opioids.

h. The Joint Commission

- i. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), often simply referred to as “The Joint

¹³⁷ PPLPC017000046138 at 6156.

¹³⁸ West Virginia Attorney General, “Best Practices for Prescribing Opioids in West Virginia,” pp. 1, 2, <http://ago.wv.gov/Documents/2016.08.19%20BP%20Prescribing.PDF>. (emphasis added.)

Commission” (TJC), is a United States-based nonprofit tax-exempt 501(c) organization that accredits health care organizations and programs in the United States. The Joint Commission arose out of a movement in the 1950s to reform hospitals by looking at whether or not patients got better. JCAHO went through a consolidation of power over the years, combining multiple medical organizations under one roof, simplifying its name in 2007 to “The Joint Commission.” Its positioning statement is “Helping Health Care Organizations Help Patients.”¹³⁹

- ii. Today, having Joint Commission accreditation is required for many hospitals and clinics to remain licensed. Payment for services from the Centers for Medicare and Medicaid Services (CMS), the largest federally funded insurance program, is also contingent on TJC approval. TJC approval is obtained through periodic surveys.
- iii. In 2001, the Joint Commission made pain the fifth vital sign, alongside heart rate, temperature, respiratory rate, and blood pressure, and promoted the use of the Visual Analog Scale (VAS), a series of happy or sad faces supposedly corresponding to pain levels from 0 (no pain) to 10 (the most extreme pain).¹⁴⁰ The Joint Commission’s actions followed the prior advocacy of the “vital sign” campaign, that originated with the APS in 1995, as described above. The Joint Commission sold educational materials to hospitals so they could meet the standards of pain treatment that would be required to pass the next Joint Commission Survey. These materials included laminated cards and posters of the Visual Analog Scale of pain, as well as teaching videos promoting more liberal prescribing of opioids for pain, including misleading statements such as: “Some clinicians have inaccurate and exaggerated concerns about addiction, tolerance and risk of death. . . . This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control.”¹⁴¹ Per the GAO 2003 report,

¹³⁹ The Joint Commission, <http://www.jointcommission.org/>.

¹⁴⁰ Lembke, ”Drug Dealer MD”, fn. 2, above, at p. 66.

¹⁴¹ Catan T, Perez E., A Pain Drug Champion Has Second Thoughts. *The Wall Street Journal*. December 2012, at p.4.

“During 2001 and 2002, Purdue funded a series of nine programs throughout the country to educate hospital physicians and staff on how to comply with JCAHO’s pain standards for hospitals and to discuss postoperative pain treatment. Purdue was one of only two drug companies that provided funding for JCAHO’s pain management educational programs. Under an agreement with JCAHO, Purdue was the only drug company allowed to distribute certain educational videos and a book about pain management; these materials were also available for purchase from JCAHO’s Web site. Purdue’s participation in these activities with JCAHO may have facilitated its access to hospitals to promote OxyContin.”

- iv. On December 31, 2000, an internal Purdue email from Robin Hogen to Mortimer Sackler, MD, responded to Dr. Sackler’s assertion that more articles were needed “to help counteract the negative articles in the national media.” Hogen’s email, regarding press coverage of JCAHO pain guidelines, stated, “With respect to generating more articles about pain guidelines, we ‘loaned’ JCAHO our PR firm (Fleishman Hillard) last year during the national roll out of the new standards. I suspect some of these stories which are now breaking at year-end were generated by media contacts made several months ago. We could certainly renew that grant (\$75k) this year- to generate as much positive, unbranded publicity about the new pain standards and the chronic undertreatment of pain in America. Good idea.” This exchange supports my opinion that the Pharmaceutical Opioid Industry played a significant, insidious role in the epidemic of over-prescribing of opioids, by funding the widespread promotion of standards that mandated pain treatment, while the medical profession and the public were unaware of Industry’s hidden role.¹⁴²
- v. As noted above, J&J and Janssen worked with the RWJF to support the Wisconsin PPSG. These entities also worked together to provide funding to The Joint Commission (JCAHO).
- vi. The JCAHO and PPSG, financially supported by Janssen and RWJF, were instrumental in creating new pain treatment standards

¹⁴² PDD8801183361 at 3363.

that promoted increased opioid use as well as opioid-friendly prescribing guidelines in the early 2000's.

- vii. A recent study shows that the Pharmaceutical Opioid Industry continues to spend vast amounts of money to promote their products and “consulting” relationships with influential doctors and educators. An analysis of CMS Open Payment data for non-research payments by companies marketing opioids to teaching hospitals from 2013-2018 found that “[o]verall, there were 444 payments linked to opioid products totaling \$7,023,140 (median value of individual payment \$1348; IQR \$245 to \$20,291)... In addition to payments linked to opioids, we identified 5,168 payments made by 22 companies marketing opioids which were not linked to any opioid or non-opioid product; the total value of these payments was \$120.0 million.”¹⁴³ Of the \$7 million linked to specific opioid products, \$3.7 million of that was for “consulting fees”.¹⁴⁴ The products promoted at teaching hospitals include Endo’s Opana, Purdue’s OxyContin, Hysingla and Butrans and Janssen’s Nucynta.¹⁴⁵
 - viii. My opinions stated above are consistent with, and supported by, the ASPPH Report referenced above, which found, “The medical community became more aggressive in its use of opioids in response to a multi-faceted Pharmaceutical Opioid Industry - funded campaign that downplayed opioid risks and exaggerated benefits,” and that “the opioid crisis was caused largely by deceptive marketing.”¹⁴⁶ The ASPPH Report also stated, “The opioid crisis can be directly tied to practices adopted and encouraged by opioid manufacturers and distributors. As such, the industry’s credibility is near zero”¹⁴⁷
- i. Examples of Misrepresentations: “Pseudoaddiction” and “Breakthrough Pain”

¹⁴³ Anderson TS et al. Financial payments to teaching hospitals by companies marketing opioids. *J. General Internal Medicine* (2019), at p. 1.

¹⁴⁴ *Id.* at Table 2.

¹⁴⁵ *Id.* at Table 1.

¹⁴⁶ ASPPH Report, “Bringing Science”, fn. 15, above, at p. 7; emphasis added.

¹⁴⁷ *Id.* at 32.

- i. The Pharmaceutical Opioid Industry created promotional material misrepresented as educational material, and disseminated this mis-education through all the modalities described above, from key opinion leaders, to continuing medical education, to professional medical societies, to the Pain and Policy Study Group, to the Federation of State Medical Boards, to The Joint Commission. Misleading concepts such as “pseudoaddiction” and “breakthrough pain” provide two prominent examples.
- ii. Defendants mischaracterized addictive behavior as “pseudoaddiction.”
 - A. Based on a single case report of a patient who engaged in drug-seeking behavior,¹⁴⁸ doctors were encouraged to conceptualize the patient’s addictive behavior as evidence of under-treated pain. This case report was co-authored by David Haddox. The authors of the case report incorrectly asserted that treatment of pain is often inadequate because of “excessive fears of tolerance and dependence by both health professionals and the public,”¹⁴⁹ when in fact those fears were well-justified and should have been respected. In addition, since the conditions of addiction and dependence are common, their recommended treatment to continue administering or even increase opioids despite addictive behavior, undoubtedly put more patients at risk of becoming addicted or dependent.
 - B. There is no such thing as “pseudoaddiction,” and no evidence that providing more opioids is an appropriate response to patients exhibiting drug-seeking behavior. On the contrary, tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication, not increasing its dose.

¹⁴⁸ Weissman DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome. *Pain*. 1989; 36(3):363-366.
<http://www.ncbi.nlm.nih.gov/pubmed/2710565>.

¹⁴⁹ *Id.* at p. 365.

- C. In a review article on use of the term “pseudoaddiction,” the authors found, “By 2014, pseudoaddiction was discussed in 224 articles. Only 18 of these articles contributed to or questioned pseudoaddiction from an anecdotal or theoretical standpoint, and none empirically tested or confirmed its existence. Twelve of these articles, including all four that acknowledged pharmaceutical funding, were proponents of pseudoaddiction. In contrast, six articles, none with pharmaceutical support, questioned pseudoaddiction as a clinical construct.”¹⁵⁰ Further, the authors wrote, “In conclusion, we find no empirical evidence yet exists to justify a clinical ‘diagnosis’ of pseudoaddiction.”¹⁵¹ I agree that there is no empirical evidence to justify a diagnosis of pseudoaddiction, and that use of this term was spread by the manufacturers of prescription opioids, with the explicit and dangerous message to doctors that more opioids should be prescribed.

- D. To “correctly define addiction” the Pain and Policy Study Group (PPSG), discussed above, took consensus definitions from the Pharmaceutical-Opioid-Industry-funded American Society of Addiction Medicine, American Academy of Pain Medicine, and the American Pain Society.¹⁵² Those included a definition of the term pseudoaddiction: “Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may ‘clock watch,’ and may otherwise seem inappropriately ‘drug seeking.’ Even such behaviors as illicit drug use and deception can occur in the patient’s efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when pain is effectively treated.”¹⁵³ Thus, PPSG,

¹⁵⁰ Greene MS, Chambers RA. Pseudoaddiction : Fact or Fiction ? An Investigation of the Medical Literature. *Curr Addict Rep* 2015;310-317. doi:10.1007/s40429-015-0074-7, at p. 310.

¹⁵¹ *Id.* at p. 314.

¹⁵² WIS_PPSG_002042, June 8, 2001.

¹⁵³ *Id.*

an entity funded by the Pharmaceutical Opioid Industry, aligned with and promoted the Industry-supported view of “pseudoaddiction” as a real diagnosis for which more opioids were the prescribed treatment. (See Appendix II to this report). Dr. Portenoy later criticized the Pharmaceutical Opioid Industry’s use of the term pseudoaddiction.¹⁵⁴

- E. The 1998 Industry-influenced guidelines of the Federation of State Medical Boards, discussed above, incorporate the concept of pseudoaddiction,¹⁵⁵ providing further evidence of industry’s influence over the FSMB.

iii. Defendants mischaracterized tolerance as “breakthrough pain.”

- A. “Breakthrough pain” is a supposedly heightened state of intermittent pain that exceeded the analgesic capacity of the patients’ underlying chronic opioid dose. On the contrary, ‘breakthrough pain’ is far more likely to represent the patients’ declining response to their prescribed opioids due to the well-established effect of tolerance, whereby a greater opioid dose is needed to attain the same effect over time; thus the addition of ACTIQ or other opioids for so-called “breakthrough pain” represented an increased opioid dose that added to patients’ risk of adverse effects.
- B. Tolerance is the need for more and more of the drug to get the same effect. As the dose is increased to overcome tolerance to the pain relieving effects of the drug, patients are exposed to the other dose-dependent risks associated with the drugs, including the risk of death. Furthermore, tolerance to the respiratory suppressant effects (the ability of opioids to decrease breathing rate and thus blood oxygenation) develops more slowly than tolerance to the pain-relieving effects of the drug. As such, as the dose of opioids goes up to target pain relief, the breathing rate goes

¹⁵⁴ Declaration of Russell K. Portenoy, M.D. in MDL 2804, at ¶ 44.

¹⁵⁵ Federation of State Medical Boards. *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain* (May 2, 1988), https://painpolicy.iu.edu/sites/default/files/sites/www.painpolicy.wisc.edu/files/model_0.pdf.

down, increasing the risk of accidental overdose and death.¹⁵⁶ Tolerance is not a short-lived phenomenon. It persists and renders the opioid largely ineffective for the underlying pain condition. Despite tolerance, patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving the pain of opioid withdrawal from the previous dose.

- C. Once tolerance occurs, patients may experience opioid withdrawal multiple times a day between pain pill doses, and need higher and higher doses to avoid between-pill withdrawal. Tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication. Instead, in the 1990's and early 2000s, Defendants' promotional messages advised doctors that tolerance should be addressed by adding short-acting opioids to long-acting opioids for "breakthrough pain", or by "rotating" to another opioid.
- D. As explained more fully in Appendix I.B. to this Report, Defendants marketed opioids such as ACTIQ as "the ideal agent" for breakthrough chronic pain.¹⁵⁷ This promotional message was misleading and contributed to opioid over-exposure.

5. Opioid distributors collaborated with opioid manufacturers and pharmacies to promote sales of opioid pain pills. Such coordinated efforts included programs to give away free samples of opioids; coupons to discount opioids; and promotion of specific opioid products under the guise of education. These activities increased the population of opioid users, dose and duration of opioid use, and the risk of opioid misuse, addiction, dependence, and death.

- a. Opioid distributors worked in close collaboration with opioid manufacturers and pharmacies to promote sales of opioid pain pills. The

¹⁵⁶ Lembke, *et al.*, "Weighing the Risks," fn.4, above, at p. 987; Chou, *et al.*, "Effectiveness and Risks," fn. 204, below, at p. ES-25.

¹⁵⁷ TEVA_CAOC_00759630 at 9633.

claim that Distributors were indifferent transporters of opioid pain pills between Manufacturers and Pharmacies ('We're just the trucks') is refuted by the many documents demonstrating a coordinated partnership to promote prescription opioid consumption, as well as a quid pro quo reimbursement structure. At every step in the supply chain, money flowed. There was a coordinated, psychologically sophisticated effort which appeared on its face to be about helping patients save money, 'overcome barriers,' and 'adhere to medical treatment,' but was in fact an elaborate scheme designed to promote sales of specific opioid products.

- b. Distributors, Manufacturers, and Pharmacies collaborated to offer free and discounted samples of dangerous and addictive opioids. As any drug dealer can tell you,¹⁵⁸ free samples are a tried and true way to hook consumers and secure future sales. Further, once patients become dependent on opioids, their continued consumption is income and price sensitive, making them vulnerable to discounted products. "An extensive account of addiction as a rational response weighing marginal benefits and marginal costs of consumption has been modeled in the economic literature (Stigler & Becker, 1977; Becker & Murphy, 1988; Chaloupka, 1991; Iaccone, 1986). When a reduction in income is anticipated, it is predicted that consumption will decrease. When subsidies are eliminated, the reaction is similar to a decrease in income."¹⁵⁹ By offering free samples for prescription opioids, the Opioid Pharmaceutical Industry created customers in the form of opioid-dependent patients, and then kept them coming back with discounted prices. I observed these economic factors exert their influence among my own patients. Prescription opioids and illicit heroin/fentanyl are interchangeable in terms of their addictive and euphoric effects, and my patients would commonly use whichever opioid was more readily available at the lowest price.
 - i. McKesson collaborated with Janssen to give away free fentanyl, an opioid that is 50 times more potent than heroin. Branded advertisements promoted the free-give-away of 5 x 25 mcg

¹⁵⁸ "Drug Dealer Admits to Giving Free Sample." https://www.herald-dispatch.com/news/drug-dealer-admits-to-giving-free-sample/article_ce289f74-e9c3-58ce-8cce-d7483e774627.html; dealer "admitted he provided the free sample of drugs to secure future sales..."

¹⁵⁹ Roddy J, Steinmiller CL, Greenwald MK. Heroin purchasing is income and price sensitive. *Psychol Addict Behav.* 2011;25(2):358-364. doi:10.1037/a0022631

Duragesic fentanyl patches, claimed by submitting a voucher to McKesson.¹⁶⁰

- ii. The coordinated collaboration did not end there. On the back end, Janssen trained its sales reps to promote the free fentanyl patches to doctors, with language as follows:
 - A. “Physicians may be more inclined to try Duragesic because patients are now able to ‘sample’ Duragesic free of charge.”¹⁶¹
 - B. “Sell the coupons like they are a third product and close for action. ‘Dr. Smith, do you feel that the Duragesic coupons will be helpful to you and your patients when you are ready to convert to a long acting, because they can try Duragesic for free?’”¹⁶²
 - C. “Pull out one coupon from the pack and explain each section of the coupon Explain that one coupon is good for one free box of five patches, which is fifteen days of treatment. Remind the doctors that the coupon must be accompanied by a written prescription.”¹⁶³
 - D. “Display the coupons in a prominent place for easy access and to help remind the doctors of the program. It is very important to explain to the staff that you will replenish their coupon supply every month. This is very important so the doctors do not save the coupons for special patients.”¹⁶⁴
 - E. “Be very enthusiastic about the coupons! Make the physicians feel special because they are a part of only a select few that have the opportunity to participate in this coupon program.”¹⁶⁵

¹⁶⁰ MCKMDL00334317

¹⁶¹ JAN-TX-00066294.

¹⁶² *Id.*

¹⁶³ *Id.*

¹⁶⁴ *Id.*

¹⁶⁵ *Id.* (emphasis in original)

- F. “I respond [to the doctor expressing reservations] by saying, ‘I believe that a patient in true chronic pain will try anything that you prescribe for them, because all the [sic] they want is pain relief. So, why not use a coupon that allows the patient to try Duragesic for free! You and the patient have nothing to lose.’”¹⁶⁶
- iii. McKesson partnered with Janssen to give away free and discounted Nucynta and Nucynta ER.
- A. A “Nucynta ER/Nucynta New 10 Free Pills Program” from September 1, 2011 to December 31, 2012, gave patients free drug.¹⁶⁷ Per this document, where the “10 Free Pills” program was in place, “Average monthly claims [went] up 198% over 2011.”¹⁶⁸ When an older “10 Free Pills” program was phased out, Nucynta claims went down.¹⁶⁹
- iv. 2011 Purdue Dear HC Professional (McKesson): McKesson partnered with Purdue to distribute a “Butrans Savings Card.”¹⁷⁰
- c. Opioid Distributors collaborated with Opioid Manufacturers to advertise specific opioid products.
 - i. AmerisourceBergen collaborated with Janssen to advertise Nucynta for a fee of [REDACTED] for a 2 week marketing campaign: “Horizontal Banner Ad on ABC Order, the new product ordering and communication platform for AmerisourceBergen Drug Corporation customers.”¹⁷¹
 - ii. McKesson partnered with TEVA to promote ACTIQ and FENTORA including an agreement to “distribute three (3) e-mail messages promoting the products identified below to 7,000 retail

¹⁶⁶ JAN-TX-00066294 at 6295.

¹⁶⁷ JAN-MS-01071368 at 1399.

¹⁶⁸ JAN-MS-01071368 at 1401.

¹⁶⁹ JAN-MS-01071368 at 1408.

¹⁷⁰ Purdue Pharma Butrans Product Alert, September 2011, http://rphmail.com/ch/2011/butrans_101411.html

¹⁷¹ ABDCMDL00002828

pharmacy recipients” and “four hundred sixty three (463) mailers to our top Independent Pharmacies.”¹⁷²

- iii. Cardinal Health partnered with TEVA to promote TEVA products. Cardinal Health agreed to distribute, at Teva’s request, “one (1) e-mail communication to approximately 105,000 retail pharmacists and pharmacy technicians in Cardinal Health’s eConnection program database that includes information on the CII product launch.”¹⁷³ And “The communication distributed by Cardinal Health will be prepared by Teva in accordance with the specifications set forth below.”¹⁷⁴ Content “May include product benefits, ordering information and website links. Teva to provide the message to appear in the subject line of the email communication.” “The cost to distribute the above one (1) e-mail communication shall be [REDACTED]¹⁷⁵
 - iv. Cardinal Health partnered with Actavis to promote Kadian.¹⁷⁶
 - v. McKesson Specialty Health Pharmaceutical & Biotech Solutions, LP, collaborated with Purdue Pharma to advertise Butrans Transdermal System in October 2016, for a fee of [REDACTED]. McKesson “agrees to post Supplier’s graphical ad with a link to Supplier’s Supplier Product website (<https://www.butrans.com>), on McKesson’s online ordering portal, McKesson Connect. The graphical ad will be posted for a total of four (4) weeks.”¹⁷⁷
 - vi. AmerisourceBergen partnered with Purdue in 2008 to promote Oxycontin’s “new items and the Rebate program”.¹⁷⁸
- d. Opioid Distributors used sophisticated psychological methods to target patients directly. McKesson trained pharmacists in Motivational

¹⁷² MCKMDL00353368 at3368.

¹⁷³ CAH_MDL2804_00132726 at 2727.

¹⁷⁴ *Id.*

¹⁷⁵ *Id.*

¹⁷⁶ ACTAVIS0220239

¹⁷⁷ MCKMDL00353277

¹⁷⁸ PPLPC004000146529 at 6530.

Interviewing,¹⁷⁹ a form of individual psychotherapy originally conceived to help addicted patients get into recovery. It is ironic that the Opioid Pharmaceutical Industry used (is using) these techniques to get patients to continue to take opioids, under the guise of promoting ‘medication adherence.’

- i. In 2012, McKesson collaborated with Janssen to promote Nucynta directly to customers using a phone program and face to face Motivational Interviewing at the “pharmacy counter.”¹⁸⁰
- ii. McKesson’s Pharmacy Intervention Program’s stated goal was to “Increase patient adherence to prescribed drug therapy through a series of targeted ‘behavioral modification’ counseling sessions delivered at the pharmacy counter”¹⁸¹ and a “Comprehensive McKesson team assembled to support pharmacy execution.”¹⁸²
- iii. Of note, this intervention includes training pharmacists in Motivational Interviewing (MI), an advanced psychologic method of persuasion first developed to treat addiction. The pharmacies, in turn, were reimbursed for doing MI at “the counter.” “McKesson reimburses pharmacy for service provided.”¹⁸³ The below McKesson slide shows how the Pharmacy Intervention Program (“PIP”) worked¹⁸⁴:

¹⁷⁹ Rollnick S, Miller W. What is Motivational Interviewing? *Behavioural and Cognitive Psychotherapy*. 1995;23(4):325-334.

¹⁸⁰ JAN-MS-01071368 at 1416.

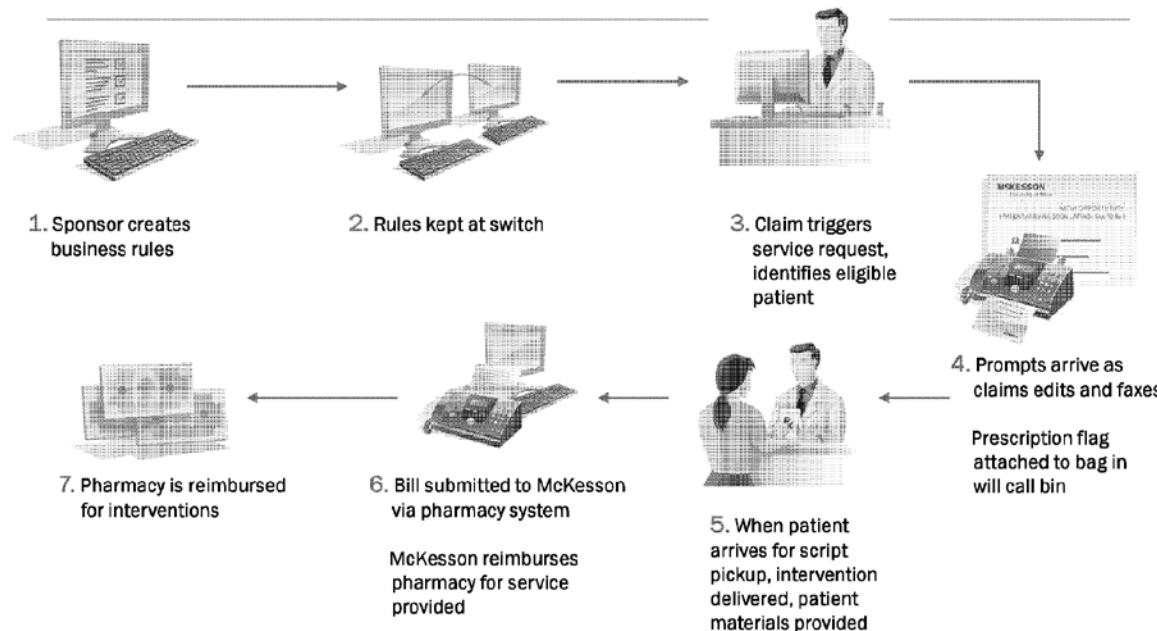
¹⁸¹ *Id.*

¹⁸² *Id.*

¹⁸³ JAN-MS-01071368 at 1417.

¹⁸⁴ *Id.*

PIP Pharmacy Workflow



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Identical

JAN-MS-01071417

- iv. Branded content was camouflaged inside non-branded ‘educational’ content in the context of Motivational Interviewing. A slide in this document, shown below, shows a column on the left labeled “Pharmacy Training/Support” which includes “Motivational Interviewing CE Coursework,” next to a column on the right labeled “Brand Specific Kit Contents” which includes the following statement: “Manufacturer sponsors may elect to provide a piece of branded patient collateral.”¹⁸⁵

¹⁸⁵ JAN-MS-01071368 at 1419.

Pharmacy Training & Support

- **Pharmacy Training/Support**

- ***Brand agnostic, provided to all participating pharmacists***

- **Motivational Interviewing CE Coursework:**

- Developed by Motivational Interviewing expert Cathy Cole, this required training provides pharmacists with a foundation in the principles of Motivational Interviewing and health behavior change.

- **Program Kit:** Focuses on the clinical and operational aspects of the program. Provides pharmacy staff with workflow training and support tools along with additional background information on Motivational Interviewing.

- **Adherence Advisor:**

- Monthly adherence newsletter distributed exclusively to Patient Outreach Network pharmacies.

- **PON Call Center Team:**

- Dedicated inbound and outbound team of expert callers who provide support for PIP pharmacies.

- **Brand Specific Kit Contents**

- ***Delivered to pharmacies prior to launch of a new brand***

- **Product Kit Cover Letter:**

- Provides overview of materials included in brand kit. Features brand specific program information, counseling tips and information about adverse event reporting.

- **Pharmacist Consultation Aid**

- This laminated one page guide provides brand specific information to guide the adherence counseling session.

- **Product-Specific Clinical Information**

- Manufacturer sponsors may elect to provide a piece of branded patient collateral



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- v. In 2013, McKesson promoted its Pharmacy Intervention Program by letting Purdue know about their “Pharmacy Brand Kit,” whereby Purdue could promote its product under the guise of education: “The Brand Specific Pharmacy Kit is mailed to each participating pharmacies prior to launch. This kit includes a Cover Letter and Coaching Guide. Purdue will have the opportunity to participate in the development and review all pharmacy materials specific to their program. The brand kit can also include any additional resources the pharmacist should read as well as patient brochures to hand out during the coaching session (Purdue would develop and provide).”¹⁸⁶ In other

¹⁸⁶ PPLPC002000140782 at 0783.

words, the McKesson’s Pharmacy Intervention Program is a vehicle for opioid manufacturers to advertise their products.

- vi. McKesson directly targeted patients as well as pharmacists. McKesson described its “US-based, healthcare-dedicated contact center”,¹⁸⁷ which delivers “patient-centric behavioral coaching”¹⁸⁸ as part of its broader “Behavioral Call Campaign” wherein “Agents make outbound calls to patients in order to uncover personal barrier and provide appropriate messaging/content to help overcome those barriers.”¹⁸⁹ These efforts, claim McKesson, are “aligned to address Janssen’s needs.”¹⁹⁰
- vii. As described in this email exchange between Cardinal executive Leslie Arend and Covidian executive Connie Kisinger on April 12, 2013, Cardinal’s own legal team expressed reservations about ads promoting the opioid product Exalgo: “I received word late this morning that due to some things with the DEA, our legal team made several changes to marketing programs with controlled substances. While we can feature Exalgo on the ordering platform, it was deemed that it could only be prompted by a search key word of ‘Exalgo’. The reason for this is legal has said that the pharmacist must actually be searching for the product in order to show the advertisement otherwise it may seem as though Cardinal Health is ‘pushing’ a controlled substance.”¹⁹¹
- viii. This document details how Purdue and McKesson proposed to thwart a trend they observed in 2013 in which patients were discontinuing opioids.¹⁹² Many patients on opioids at this time had good medical reasons for

¹⁸⁷ JAN-MS-01071368 at 1428.

¹⁸⁸ *Id.* at 1427.

¹⁸⁹ *Id.* at 1426.

¹⁹⁰ *Id.* at 1424.

¹⁹¹ MNK-T1_0007819281

¹⁹² PPLPC002000140782

discontinuing opioids, including adverse medical consequences and serious risk of addiction and overdose death. Instead of helping patients with this goal, McKesson promoted maintaining and even increasing doses of Butrans: “In 2013, one of our commercial goals is to reduce discontinuation and improve patient adherence.... HCPs are initiating opioid-experienced patients inappropriately on the 5 mcg/hour when they should be initiated on the 10 mcg/hour. These factors are negatively impacting patient adherence, and Marketing would like to execute the McKesson Pharmacy Intervention Program in order to reduce the Butrans discontinuation rate.”¹⁹³ This is another example of how Manufacturers and Distributors used ‘improving patient adherence’ as a proxy for boosting sales of a specific branded product.

6. No reliable scientific evidence shows that long-term opioid therapy is effective for chronic non-cancer pain.

- a. Through the aforementioned methods, and by relying on flawed and industry-backed studies, the Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree.
- b. The best evidence available suggests that there is little or no improvement in pain or function for most patients on long-term opioid therapy. The Industry further claimed that the failure to prescribe opioids led to the “undertreatment of pain.” Whether or not pain was undertreated does not change the fact that prescription opioids are an inappropriate method to address that concern, due to the absence of evidence of long-term benefit, and the strong evidence of unacceptable risk.¹⁹⁴ Patients often endorse ongoing subjective benefit from the opioid, not because it is treating

¹⁹³ *Id.*

¹⁹⁴ As stated in the NASEM 2017 Report, “The very real problems of underdiagnosis and undertreatment of pain are valid concerns, but *it would be a mistake to infer that greater utilization of opioids would ameliorate these problems,*” due to the lack of evidence that opioids provide long-term benefits for chronic pain. NASEM Report (2017), fn. 42, above, at p. 51. (emphasis added).

underlying pain, but because it is relieving the pain of opioid withdrawal from the previous dose. Studies show that pain improves when patients on chronic high dose opioid therapy reduce their dose or come off opioids. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment.

- c. Scientific evidence of prescription opioids' benefit for chronic pain has been repeatedly described as "weak," or "inconclusive." Randomized, placebo-controlled clinical trials, generally 12 weeks or less, were too brief to support claims of long-term benefit, and non-randomized trials do not provide reliable evidence of efficacy. Such evidence was inadequate to support the widespread use of the drugs and the risks they imposed. Even the 2009 Guidelines promulgated by advocacy groups funded by the Pharmaceutical Opioid Industry admitted that evidence regarding chronic opioid therapy was "insufficient to assess effects on health outcomes."¹⁹⁵ Twelve-week studies of opioids are insufficient to assess their risks and benefits, for the following reasons:
 - i. Prescription opioids differ from other pain medications in important ways. In addition to providing acute pain relief, opioids also have unintended psychotropic effects (improved mood, increased energy, decreased anxiety), which make them more likely to be reinforcing and to lead to addiction. Patients with chronic pain can find opioids reinforcing, independent of whether they provide pain relief.¹⁹⁶ Although addiction to opioid painkillers can occur quickly in some individuals, for others, addiction may take weeks, months, or years to manifest, and duration of exposure is the most significant risk factor for addiction (*see* discussion of Edlund study, above). Hence, a true assessment of the risks of highly addictive drugs like opioid pain relievers (the molecular equivalent of heroin) requires a longer period of study than 12 weeks.

¹⁹⁵ Chou R. Clinical Guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Journal of Pain*. 2009;10(2):113-130 at p. 130.e5.

¹⁹⁶ Matthias M, Donaldson MT, Jensen AC, Krebs EE. "I was a little surprised": Qualitative Insights from Patients Enrolled in a 12-Month Trial Comparing Opioids to Non-Opioid Medications for Chronic Musculoskeletal Pain. *J Pain*. 2018; 1-9, at p. 1.

- ii. According to a study of combat injury victims among military personnel, 6.8% developed an opioid addiction after a short-term prescription of opioids (within a 7-day discharge window). The median time to diagnosis of the opioid use disorder was 3 years.¹⁹⁷ The authors state that this was “the first study to show that persistent opioid use after trauma is associated with the development of clinically recognized opioid abuse years after the initial injury.”¹⁹⁸ The long median time to diagnosis of opioid addiction reinforces the conclusion that industry-sponsored studies claiming a low risk of addiction are far too brief to provide reliable, real-world estimates of risk.¹⁹⁹
- iii. Naliboff *et al.*, in their two-arm, randomized, pragmatic clinical trial comparing stable dose to escalating dose of opioid medications among 135 patients at a VA clinic in Los Angeles, “carefully selected” as appropriate candidates for chronic opioid therapy, nevertheless discharged 27% of patients over the course of the study due to opioid misuse/noncompliance.²⁰⁰ Urine toxicology screens were included in the protocol.²⁰¹ The authors concluded, “Overall, this study confirms that even in carefully selected tertiary-care patients, substance misuse is a significant problem. Importantly, *40% of these misuse problems did not become apparent within the first 6 months, pointing out the need for studies of longer duration.*”²⁰² (emphasis added). These data also support the need for ongoing monitoring for misuse and addiction in patients prescribed opioids long-term.
- iv. There are serious and certain risks associated with long-term opioid therapy, including but not limited to tolerance, dependence, withdrawal, opioid induced hyperalgesia (increased pain caused by

¹⁹⁷ Beyer CA, Poltavskiy E, Walker LE *et. al.*, Persistent Opioid Use After Combat Injury and Subsequent Long-term Risk of Abuse: a retrospective cohort study. *Annals of Surgery*, 2019; 1-9, at p. 1.

¹⁹⁸ *Id.* at p. 3.

¹⁹⁹ See discussion of industry-sponsored studies of addiction risk at Section C.7, below.

²⁰⁰ Naliboff BD, Wu SM, Schieffer B, *et al.* A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. *J Pain*. 2011;12(2):288-296, at p. 288.

²⁰¹ *Id.* at p. 291.

²⁰² *Id.* at p. 295.

opioids), immunosuppression, serious constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, addiction, accidental overdose, and death, reflecting a low benefit to risk ratio for long-term opioid therapy.²⁰³ These risks increase with increasing dose and duration of the drug.²⁰⁴ Hence, the high risks associated with opioids necessitate a longer study period to assess the true benefit-risk ratio for all patients.

- d. A series of reviews, including several in the Cochrane Database, a collection of reviews that summarize the results of medical research, have reached similar conclusions regarding the inadequacy of the scientific evidence of long-term opioid therapy for chronic non-cancer pain.
 - i. The 2010 Cochrane Review (Noble 2010) found that there was only “weak” evidence to support the use of opioids for chronic non-cancer pain.²⁰⁵
 - A. “All of the evidence bases considered in this systematic review were of low internal validity and therefore at potentially high risk of bias.” Reasons for this assessment included the funding source (“Only two studies did not clearly have a funding source with a potential conflict of interest in the findings (*e.g.*, drug company),” failure to compare characteristics of dropouts to those of patients who completed the studies, and failure to describe recruitment methods. The highest risk of bias existed for the “continuous outcomes” of pain relief and quality of life, because ‘high attrition rates affect both the risk of bias and

²⁰³ Lembke *et al.*, “Weighing The Risks,” fn.4, above, at p. 985; *see also* Chou R, Deyo R, Devine B, *et al.* The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. *Evid Rep Technol Assess (Full Rep)*. 2014;218(218):63. doi:10.23970/AHRQEPCERTA218 at p. ES-1; *see also* Edelman EJ, Gordon KS, Crothers K, *et al.* Association of Prescribed Opioids with Increased Risk of Community-Acquired Pneumonia among Patients with and Without HIV. *JAMA Internal Medicine*. 2018, at p. 298.

²⁰⁴ Chou R, Turner J a., Devine EB, *et al.* The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015;162(4). doi:10.7326/M14-2559, p. 283.

²⁰⁵ Noble M, Treadwell JR, Tregear SJ, *et al.* Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010;(1):CD006605. doi:10.1002/14651858.CD006605.pub2, p. 2.

the generalizability of the results from the continuous data outcomes.”²⁰⁶

- B. At pp. 9-14, specific data on attrition were provided: For the “strong opioid” category (categories described at p. 7), including extended release morphine, controlled release oxycodone, extended release oxymorphone, extended release tramadol and methadone; for oral medications, 34.1% discontinued due to adverse effects²⁰⁷ and 10.3% discontinued due to insufficient pain relief²⁰⁸, for a total of 44.4% who discontinued strong oral opioids.²⁰⁹ Almost half of all study participants dropped out of the study before it was complete, yet their data was not included in the final analyses.
- C. The review states that only 273 (58%) of those who began the long-term extensions of short-term trials remained in the study at the 6-7.5 month cut-off point where data were available for all three oral opioid studies. “Because the attrition rate is so high, the participants are likely highly selected, and the data may be biased.”²¹⁰
- D. The authors report pain relief for those able to remain on oral opioids for six months; however: “The strength of the evidence supporting this conclusion is weak.”²¹¹
- E. Quality of Life (QoL):
 - I. For oral morphine: A single study (Allan, 2005), reporting a “small improvement on the mental subscale and a larger improvement of the physical

²⁰⁶ *Id.* at pp. 7-8.

²⁰⁷ *Id.* at p. 10

²⁰⁸ *Id.* at p. 13.

²⁰⁹ *Id.* at pp. 9-14.

²¹⁰ *Id.* at p. 15.

²¹¹ *Id.* at p. 16.

subscale” provided an “insufficient quantity of data from which to draw conclusions.”²¹²

- II. QoL improvement was “weakly supported” with transdermal fentanyl (TDF).²¹³ For QoL with intrathecal opioids, there were inconsistent findings “No conclusions can be drawn.”²¹⁴
- F. “Data describing long-term safety and efficacy of opioids for CNCP [chronic non-cancer pain] are limited in terms of quantity and quality. An evidence base consisting of low-quality studies provides only *weak evidence* from which to draw qualitative conclusions and only low-stability evidence from which to draw quantitative conclusions.”²¹⁵ (Emphasis added.)
- G. “Despite the identification of 26 treatment groups with 4,768 participants, the evidence regarding the effectiveness of long-term therapy in CNCP was too sparse to draw firm conclusions.”²¹⁶
- ii. Another Cochrane Review of opioids in the treatment of chronic low back pain (CLBP) (Chaparro 2013) found, “There is some evidence (*very low to moderate quality*) for short-term efficacy (for both pain and function) of opioids to treat CLBP compared to placebo.”²¹⁷ (emphasis in original). Yet the authors make clear there is little or no evidence of opioid efficacy long-term.
- A. “There are no placebo-RCTs supporting the effectiveness and safety of long-term opioid therapy for treatment of

²¹² *Id.* at p. 20.

²¹³ *Id.* at p. 21.

²¹⁴ *Id.* at p. 22.

²¹⁵ *Id.* at p. 23.

²¹⁶ *Id.* at p. 25.

²¹⁷ Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database Syst Rev. 2013.
doi:10.1002/14651858.CD004959.pub4, at p. 2

CLBP We have no information from randomized controlled trials supporting the efficacy and safety of opioids used for more than four months. Furthermore, the current literature does not support that opioids are more effective than other groups of analgesics for LBP such as anti-inflammatories or anti-depressants.”²¹⁸

B. “The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. The initiation of a trial of opioids for long-term management should be done with extreme caution, especially after a comprehensive assessment of potential risks.”²¹⁹

- iii. Another Cochrane review (McNicol 2013) found: “While intermediate term studies all indicated that opioids were better than placebo, most studies were small, most were short, and none used methods known to be unbiased. All these features are likely to make effects of opioids look better in clinical trials than they are in clinical practice.”²²⁰ Note that the McNicol review defined “intermediate” term studies as 35-84 days (*i.e.*, 5-12 weeks). Accordingly, these so-called intermediate studies are actually 12 weeks or less, therefore too brief to provide data relevant to efficacy for chronic pain, typically defined as lasting 12 weeks or more.²²¹
- iv. Another 2014 Cochrane Review reached similar conclusions: “Similar to previous systematic reviews of randomized trials on opioid therapy for non-cancer pain [cites omitted], we found that

²¹⁸ *Id.*

²¹⁹ *Id.*

²²⁰ McNicol E, Midbari A, Eisenberg E. Opioids for neuropathic pain (Review). *Cochrane Database Syst Rev*. 2013. doi:10.1002/14651858.CD006146.pub2, at p. 3

²²¹ *Id.* at p. 13.

most of the trials included in our review had a treatment duration of several days or a few weeks only.”²²²

- A. “Although some of the newer trials in the update had slightly longer treatment durations [cites omitted], in none of the trials did the participants receive opioids for longer than six months. This is still too short to address the impact of opioid treatment on routine clinical practice in the treatment of a chronic condition such as osteoarthritis. While no evidence of long-term effects is available from randomized trials, observational studies indicate that long-term treatment with opioids of chronic conditions such as osteoarthritis may have deleterious effects and do not seem to improve pain relief [citation omitted].”²²³
- B. Reviewers found that the “small mean benefit” was “contrasted by significant increases in the risk of adverse events. For the pain outcome in particular, observed effects were of questionable clinical relevance since the 95% CI [confidence interval] did not include the minimally clinically important difference” of 0.9 cm on a 10 cm visual analog scale.²²⁴
- C. The 2014 Cochrane Review included studies of tapentadol, as well as several other opioids. In particular, a study of tapentadol by Afilalo, et al., was among the studies as to which the Cochrane Review found too little evidence of benefit to justify the risk.²²⁵ Afilalo compared tapentadol ER 100-250 mg twice daily against placebo or oxycodone

²²² da Costa BR, Nuesch E, Kasteler R, *et al.* Oral or transdermal opioids for osteoarthritis of the knee or hip (Cochrane Review). 2014, at p. 28.

²²³ *Id.*

²²⁴ *Id.* at p. 2. Some authors have endorsed a “Minimal Important Difference” of 1.0 cm rather than 0.9 cm on the 10 cm VAS. See e.g., Busse JW, Wang L, Kamaleldin M. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. JAMA. 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472. In either case, the salient point is that opioid therapy generally does not meet even this minimal threshold of efficacy in randomized clinical trials, which makes the extraordinary risks of opioid therapy all the more unacceptable.

²²⁵ da Costa, “Oral or transdermal” fn. 222, above, at p. 15.

CR 20-50 mg twice daily.²²⁶ The primary, pre-specified endpoint of the study was changes from baseline Average Pain Intensity (API) as measured on an 11-point numerical rating scale (NRS).²²⁷ The Afilalo study was funded by Johnson and Johnson, and 9 of the 10 listed authors were employed by either J&J or Grunenthal (the German entity that developed tapentadol).²²⁸

- D. To correctly interpret the results of an efficacy study, it is important to distinguish between “statistical significance,” a numerical calculation, and “clinical significance,” which addresses the question of whether a patient experiences a noticeable beneficial difference with the treatment under investigation. Contrary to the practice of setting a pre-specified, “minimal clinically important difference” by which to assess relevant changes, as described in the Cochrane review (above), the Afilalo study did not establish such a standard. Instead, the authors reported “statistically significant” reduced average pain intensity for tapentadol compared to placebo, although the API difference between tapentadol and placebo was only 0.7 cm,²²⁹ which fails to meet the test of a minimally clinically important difference. That this study failed to mention the lack of a *clinically* significant difference between tapentadol and placebo for the primary, prespecified endpoint, suggests the possibility of bias in reporting.²³⁰

²²⁶ Afilalo M, *et al.* Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee *Clin. Drug Investig* 2010; 30:489-505.

²²⁷ Tapentadol (CG5503), Clinical Trials.Gov (last updated Apr. 18, 2012), <https://clinicaltrials.gov/ct2/show/NCT00421928>.

²²⁸ Afilalo, “Efficacy and Safety”, fn. 226, above, at p. 503.

²²⁹ *Id.* at 489.

²³⁰ The authors emphasized a claim of “clinical” significance based on a statistically significant result for one of six secondary endpoints, that is, the proportion of subjects reporting more than 50% improvement in pain intensity from baseline. Tapentadol (CG5503), Clinical Trials.Gov (last updated Apr. 18, 2012), <https://clinicaltrials.gov/ct2/show/NCT00421928>. However, the Afilalo study made no adjustment to impose a more strict test of significance due to testing of multiple endpoints.

- E. In 2015, Janssen and Grunenthal funded a study by Buynak et al purporting to evaluate the long-term efficacy of tapentadol ER among subjects with osteoarthritis or low back pain, who had completed one of four underlying, manufacturer-sponsored studies, one of which was the Afilalo study described above.²³¹ The Buynak 2015 article does not state that the underlying studies failed to meet the accepted standard for a Minimally Important Difference from placebo (Afilalo 2010, -0.7 cm; Buynak 2010, -0.8 cm; Lange 2010, -0.6 cm).
- F. As noted in the Cochrane Review (2010), above, the highest risk of bias occurs in opioid studies for the “continuous outcomes” such as pain relief because high attrition rates affect the risk of bias and the generalizability of the results. The tapentadol studies described above suffer from such bias, in that (1) the underlying studies all experienced significant dropout rates (only 57.3%, 52.2%, 56.5% and 46.2% of the tapentadol subjects completed the Afilalo, Buynak 2010, Lange, and Wild studies, respectively); and (2) only 60.5% of the subjects completed the study analyzed in the 2015 Buynak article,²³² even though the population that entered the latter study consisted of the subset of subjects who had successfully completed the prior trials. In each study, adverse events and lack of efficacy were leading reasons for failure to complete the study.

²³¹ Buynak R et al., Long-term safety and efficacy of tapentadol extended release following up to 2 years of treatment in patients with moderate to severe, chronic pain: results of an open-label extension trial. *Clin. Ther.* 2015; 37:2420-2438. In addition to the Afilalo study, the Buynak (2015) article analyzed data for patients from prior manufacturer-sponsored studies by Buynak R. et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo-and active-controlled phase III study. *Expert Opin. Pharmacother.* 2010; 11:1787-1804; Lange B, et al., Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. *Adv. Ther* 2010; 27:381-399); Wild JE, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Practice* 2010; 10:416-427. The Wild study did not include a placebo group and thus provided no data regarding difference in average pain intensity between tapentadol and placebo.

²³² Buynak, “Long-term safety”, fn. 231, above, at p. 2424.

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- v. Chou *et al.* in their 2015 systematic review on the effectiveness of opioids in the treatment of chronic pain stated: “Evidence is *insufficient* to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms.”²³³ The authors reported that most placebo-controlled studies were less than 6 weeks, and none were over 16 weeks long. “We did not include uncontrolled studies for these outcomes; reliable conclusions cannot be drawn from such studies because of the lack of non-opioid comparison group and heterogeneity of the results.”²³⁴
- vi. In 2009, Chou was the lead author of a panel made up of a majority of Industry-funded physicians and psychologists who promulgated Guidelines that allowed for the use of chronic opioid therapy; in the same publication, those authors admitted that evidence regarding chronic opioid therapy was “insufficient to assess effects on health outcomes.”²³⁵
- vii. In another systematic review of opioid and non-opioid medication for acute or chronic low back pain, Chou *et al.* found that evidence for opioids “remains limited to short term trials showing modest effects versus placebo for chronic low back pain.”²³⁶ Shortcomings of the studies included high attrition (30-60% in most trials) and “short follow-up” (one at 16 weeks, all others shorter).²³⁷ Authors also noted: “Trials were not designed to assess the risk for overdose or opioid use disorder because of relatively small samples, short follow up, and exclusion of higher risk patients; in addition, many studies used an enriched enrollment randomized withdrawal design which could underestimate

²³³ Chou R, Turner J a., Devine EB, *et al.* The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med.* 2015;162(4). doi:10.7326/M14-2559, at p. 276 (emphasis added.)

²³⁴ *Id.* at p. 280

²³⁵ Chou, *et al.*, “Clinical Guidelines,” fn.195, above, at p. 130.e5.

²³⁶ Chou R, Deyo R, Friedly J, *et al.* Systemic pharmacologic therapies for low back pain: A systematic review for an American College of physicians clinical practice guideline. *Ann Intern Med.* 2017. doi:10.7326/M16-2458, at p. 480.

²³⁷ *Id.* at p. 483

harms.”²³⁸ (See paragraphs 6.e, below, for discussion of enriched enrollment study design).

- viii. In a systematic review and meta-analysis (Häuser, Schmerz, 2015) of open-label continuation trials up to 26 weeks in duration in patients with a variety of different chronic pain disorders, the authors state “... the risk of bias [for these studies] was high ... all studies were funded by the manufacturers of the drugs²³⁹ average pain scores are unrepresentative of patient experience and of very limited utility²⁴⁰ The positive effects of opioid in long-term open-label studies cannot be disentangled from those of co-therapies not controlled for, from unspecific (placebo) effects because of the lack of placebo group or from the spontaneous recovery because of the lack of no treatment group. The external validity of open-label extension studies was comprised [sic] by a highly selected group of patients without major medical disease or mental disorders. The self-selected group of patients who were willing to participate in the open-label extension studies does not permit a clear conclusion on the long-term efficacy of opioids in routine clinical care.”²⁴¹
- ix. At a 2001 Janssen Scientific Advisory Board, while discussing how to promote Janssen’s fentanyl patch, Duragesic, the consensus statements made it clear that funding for research would be contingent on getting results favorable to Duragesic: “If a pilot pans out we may increase funding to expand the study.”²⁴² And “The goals for EMRP studies should be explicitly stated: Janssen wants to obtain certain data and seed studies that, after completion, may be expanded by funding from other sources.”²⁴³ This is

²³⁸ *Id.* at pp. 486-487.

²³⁹ Häuser W, Bernardy K, Maier C. Long-term opioid therapy in chronic noncancer pain: A systematic review and meta-analysis of efficacy, tolerability and safety in open-label extension trials with study duration of at least 26 weeks. *Schmerz*. 2015. doi:10.1007/s00482-014-1452-0, at p. 4.

²⁴⁰ *Id.* at p. 7

²⁴¹ *Id.* at p. 8.

²⁴² JAN-MS-00481055 at 1056

²⁴³ *Id.* at 1057.

indicative of the types of bias that can arise from industry-funded studies.

- e. Many studies used an enriched enrollment randomized withdrawal (EERW) study design, an inherently biased methodology which *a priori* favors opioids over placebo. EERW design selects patients who are predisposed to tolerate and prefer opioids, and hence are not reflective of the general clinical population.
 - i. Randomized, double blind, placebo-controlled trials of 12 weeks durations or less (15 studies total) of opioids in the treatment of chronic pain used to get FDA approval, relied on enriched enrollment design (Meske *et al.* 2018),²⁴⁴ and hence were biased toward favoring opioids. Open-label continuation trials commonly included subjects who successfully completed the randomized controlled trial phase using an enriched enrollment design. Hence those who entered the open label phase included those who successfully tolerated opioids through the randomized controlled trial period, resulting in an additional layer of bias favoring opioids, and diminishing the applicability of the study results to real world conditions.
 - ii. For example, of the 295 initial subjects in the study by Caldwell *et al.* (2002) 222 subjects were assigned to opioid groups and 73 were assigned to placebo.²⁴⁵ A 4-week randomized controlled trial (RCT) preceded an open-label phase; 40% of the opioid group who participated in the RCT dropped out due to adverse effects or inadequate pain relief,²⁴⁶ and only those who lasted the full four weeks were permitted to enter the open-label phase. Of the 184 subjects who entered the open-label phase, 131 (72%) came from the opioid groups, while only 50 (28%) came from the placebo group; therefore, the open-label phase included a large majority of

²⁴⁴ Meske DS, Lawal OD, Elder H, Langberg V, Paillard F, Katz N. Efficacy of opioids versus placebo in chronic pain: A systematic review and meta-analysis of enriched enrollment randomized withdrawal trials. *J Pain Res.* 2018. doi:10.2147/JPR.S160255, at pp. 923-934.

²⁴⁵ Caldwell JR, Rapoport RJ, Davis JC, *et al.* Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: Results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage.* 2002. doi:10.1016/S0885-3924(02)00383-4, at p. 283.

²⁴⁶ *Id.* at p. 283.

subjects who had demonstrated the capability to tolerate opioids, and the study's claims of efficacy are not transferable to a real-world population. Despite the bias favoring opioid-tolerant subjects, more than half failed to complete the open-label phase; 95/181 (52.5%) discontinued.²⁴⁷

- iii. A meta-analysis of short term studies (< 6 weeks) confirmed a difference between enriched enrollment studies and non-enriched enrollment studies in terms of adverse medical consequences: "The incidence of adverse effects was noticeably different in the trials that used a classical non-EERW design from those that used the EERW design (Table 3). Among the trials with a non-EERW design, the number of reported adverse effects was 26, while among the trials with an EERW design, only eight adverse effects were reported."²⁴⁸
- f. A recent (Busse 2018) meta-analysis confirms that there are no data to show clinically significant long-term efficacy of opioids in the treatment of chronic pain.²⁴⁹
 - i. The primary study outcomes were "pain relief, physical functioning, and vomiting."²⁵⁰ The study defined the term Minimally Important Difference (MID) as "the smallest amount of improvement in a treatment outcome that patients would recognize as important."²⁵¹ The data showed that opioid therapy failed to meet the MID as to the primary outcomes of pain relief and physical functioning, as well as the secondary outcomes of emotional functioning, social functioning, or sleep quality compared to placebo.²⁵²

²⁴⁷ *Id.* at p. 286.

²⁴⁸ Furlan AD, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Res Manag.* 2011;16(5):337-351. doi:10.1155/2011/465281, at p. 347.

²⁴⁹ Busse, "Opioids for Chronic Noncancer Pain", fn. 224, above.

²⁵⁰ *Id.* at p. 2449.

²⁵¹ *Id.* at p. 2450.

²⁵² *Id.* at pp. 2451, 2455.

- ii. For pain relief, the MID was defined as 1 cm on the 10 cm Visual Analog Scale (VAS); the data showed that the difference between opioid therapy and placebo was only 0.79 cm on the VAS, thus no minimally important difference was shown.²⁵³ Despite not meeting the standard, the authors state, “Although the difference did not meet the minimally important difference of 1 cm, opioids were associated with pain relief compared to placebo . . .”²⁵⁴ A more accurate statement would be that opioids were associated with a clinically insignificant difference in pain relief, since the change did not meet the study’s own definition of a clinically significant difference. The study reported a difference of 2.80 favoring opioids over placebo on a 100-point scale for “role functioning;” however, “[w]hen restricted to trials reporting actual change, high quality evidence from 16 RCTs (5329 patients) demonstrated no association of opioids on role functioning compared to placebo.”²⁵⁵
- iii. For the primary endpoint of vomiting, the opioid subjects had more than a 4-fold greater risk in nonenrichment trials, and a 2.5 times greater risk in enrichment trials, that is, trials in which subjects were pre-selected for greater ability to tolerate opioid therapy.²⁵⁶
- iv. As for “Active Comparator” studies, the authors state: Moderate quality evidence [9 RCTs, 1431 patients] showed “no difference in the association of opioids versus nonsteroidal anti-inflammatory drugs for pain relief,” and the same was true for physical function. The only significant difference was over 4-fold greater vomiting with opioids compared to NSAIDs (RR = 4.74, p ≤ 0.001).²⁵⁷
- v. Although the goal was to assess “chronic” non-cancer pain, the authors acknowledge that “it was not possible to assess the long-term associations of opioids with chronic non-cancer pain because no trial followed up patients for longer than 6 months.”²⁵⁸ There is

²⁵³ *Id.* at p. 2451.

²⁵⁴ *Id.* at pp. 2451-2452.

²⁵⁵ *Id.* at pp. 2451, 2455.

²⁵⁶ *Id.* at p. 2455.

²⁵⁷ *Id.*

²⁵⁸ *Id.* at p. 2457.

some inconsistency in the literature about the definition of “chronic.” For example, the Cochrane Review (Noble, 2010) cites the International Association for the Study of Pain (IASP) for a definition of “pain which persists past the normal point of healing,” considered to be 3 months²⁵⁹; however, on the very next page, the Cochrane review states that it considered only studies of at least six months, which it termed “Chronic opioid use...”²⁶⁰. In any case, the Busse authors’ statement that it could not be applied to “long-term” use is an important limitation.

- vi. The Busse study states, “Studies with longer follow-up reported less relief,” which provides significant support for the reduced pain relief of opioids over time, and which buttresses the conclusion that even the minor “improvements” in pain and physical function shown in the studies compiled by Busse, which had a median of only 60 days’ follow-up,²⁶¹ cannot be extrapolated to longer term opioid use.
- vii. Over three-quarters of the studies (79%) reported receiving industry funding.²⁶²
- viii. Despite these limitations, the authors concluded: “... some patients may find the modeled proportion of 12% for achieving the minimally important difference for pain relief warrants a trial of treatment with opioids.” The figure of 12% appears to represent the difference between the percentage who reported MID pain relief on placebo (48.7%) and those who reported MID pain relief on opioid therapy (60.6%); difference = 11.9%.²⁶³
- ix. In sum, the Busse analysis stands for the proposition that, by submitting to opioid therapy, the patient incurs significant and potentially fatal risks, in exchange for “benefits” that are found to be comparable to placebo for the large majority of subjects studied.

²⁵⁹ Noble, *et al.*, “Long Term Opioid Management,” fn.205, above, at p. 2.

²⁶⁰ *Id.* at pp. 3, 6.

²⁶¹ Busse, *et al.*, “Opioids for Chronic Noncancer Pain,” fn.224, above, at p. 2451.

²⁶² *Id.* at p. 2451.

²⁶³ *Id.* at p. 2456.

- x. The pain relief MID standard adopted in the Busse study was at the low end of the spectrum of such study definitions, meaning that less improvement was required to meet the MID standard. A pooled analysis of multiple pain studies found that the average MID was 17 mm (1.7 cm) on the VAS scale, or over twice the 0.79 cm difference reported in the Busse meta-analysis.²⁶⁴ Despite the lenient standard to show a difference that patients would notice, the Busse results failed that test.
- g. The SPACE randomized clinical trial study, published in JAMA in 2018, comparing opioid and non-opioid medication in the treatment of chronic pain, is the first long-term (one year) randomized controlled trial of opioids in the treatment of moderate to severe pain, and found no benefit of opioids over non-opioid medication.²⁶⁵
 - i. The SPACE trial showed no benefit of opioids over non-opioid medication (NSAIDs, acetaminophen) in the treatment of moderate to severe chronic back, hip, or knee pain. The opioid group had significantly more adverse medication related symptoms.²⁶⁶
 - ii. The SPACE trial used a gold standard study design, as follows. It was 12 months in duration, a sufficient length to assess efficacy in the treatment of chronic pain. It included only patients not previously on long-term opioid therapy, and assessed preference for opioids prior to randomization, thereby eliminating the enriched enrollment bias evident in other studies. It used a naturalistic sample of patients in the primary care setting, including some patients with severe depression and post-traumatic stress disorder, the same patients who are often on high dose long-term opioid therapy in real-life.²⁶⁷ Participants were regularly assessed

²⁶⁴ Olsen MF, Bjerre E, Hansen MD, *et al.* Pain relief that matters to patients: Systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Med.* 2017. doi:10.1186/s12916-016-0775-3, at p. 10.

²⁶⁵ Krebs EE, Gravely A, Nugent S, *et al.* Effect of opioid vs non-opioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain the SPACE randomized clinical trial. *JAMA - J Am Med Assoc.* 2018. doi:10.1001/jama.2018.0899.

²⁶⁶ *Id.* at p. 872.

²⁶⁷ *Id.* at p. 873.

for medication misuse, including checking the prescription drug monitoring database and urine drug testing.²⁶⁸ It was not sponsored by an opioid manufacturer.²⁶⁹

- iii. It is very significant that a gold standard RCT, conducted by independent researchers and published in a leading medical journal (JAMA), reached an opposite result from those claimed by the Pharmaceutical Opioid Industry based on biased, short-term studies conducted by their own employees or paid consultants, and often published in specialty journals. The SPACE trial strongly supports my opinion that chronic opioid therapy does not provide greater long-term efficacy, rendering its high risks all the more unacceptable.
 - iv. Some patients in the non-opioid group received Tramadol, an opioid, leading to questions about the claim that non-opioids were equally effective. The number of patients receiving Tramadol was small, and Tramadol was administered as a second or third line rescue medicine, to simulate how it might be used in real-life clinical practice. The authors re-ran the data without the patients who were given Tramadol, and the results were “unchanged: over 12 months, pain-related function did not differ between groups ($P=.19$) and the nonopioid group had better pain intensity ($P=.01$).”²⁷⁰ Krebs, *et al.*, also state, “Although both groups improved, we concluded results did not support opioid initiation for chronic back pain or osteoarthritis pain because opioids did not demonstrate any treatment advantages that offset their well-known risks of death and addiction.”²⁷¹
- h. The opinion has been expressed that a 3-month study is the “standard clinical trial duration accepted by the FDA for many chronic conditions.”²⁷² However, some manufacturers have tested their pain medications in significantly longer randomized clinical trials against other

²⁶⁸ *Id.* at p. 875.

²⁶⁹ *Id.* at p. 881.

²⁷⁰ Krebs EE et al., In reply: opioids vs nonopioids for chronic back, hip or knee pain. *JAMA*. 2018;305(5): 508-509 at p. 509.

²⁷¹ *Id.*

²⁷² Meske, “Efficacy of opioids versus placebo”, fn. 244, above, at pp. 923-924.

pain relievers. For example, the VIOXX label indicates that VIOXX was tested in clinical trials of up to 86 weeks for osteoarthritis of the knee and hip, against ibuprofen;²⁷³ and the CELEBREX label states that CELEBREX was tested in clinical trials of up to 24 weeks in a rheumatoid arthritis population, as well as a 9-month clinical trial that revealed higher rates of complicated ulcers among patients taking CELEBREX plus aspirin for cardiac prophylaxis, compared to CELEBREX alone.²⁷⁴ Similarly, manufacturers of opioids could have conducted clinical trials of longer duration; if they had done so, it is likely that the results would have been comparable to those found by Krebs, that is, a higher risk of adverse events and no “treatment advantages” to offset those risks.²⁷⁵ Such early testing would have contradicted the promotion of opioids purported benefits and claims of low risks, which would have discouraged the widespread use of opioids and prevented the ensuing epidemic.

- i. Other studies have also shown that opioids are no better than non-opioids for pain treatment.
 - i. In the Cochrane Review by Chaparro, *et al.*, discussed above, opioids were not superior to non-opioids for chronic low back pain.²⁷⁶
 - ii. In a review of randomized head to head comparisons of opioids vs non-opioid pain relieving medication, non-opioids were found to be superior to opioids in terms of physical function and tolerability for short term (4-12 weeks) therapy of neuropathic, low back, and osteoarthritic pain.²⁷⁷

²⁷³ Vioxx label (2004), *see* https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21647_vioxx_lbl.pdf at p. 3

²⁷⁴ Celebrex label (2005), *see* https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020998s017lbl.pdf at pp. 4, 6-7

²⁷⁵ Krebs, “In reply”, fn. 270, above, at p. 509.

²⁷⁶ Chaparro, *et al.*, “Opioids Compared to Placebo,” fn.217, above, at p. 2.

²⁷⁷ Welsch P, Sommer C, Schiltenwolf M, Häuser W. Opioids in chronic noncancer pain—are opioids superior to non-opioid analgesics? : A systematic review and meta-analysis. *Schmerz*. 2015. doi:10.1007/s00482-014-1436-0, at p. 3.

- iii. A systematic review comparing oral NSAIDs with opioids for treatment of pain due to knee osteoarthritis over at least 8 weeks' duration found opioids were no better than NSAIDs.²⁷⁸
- j. The evidence for long-term opioid therapy for chronic non-cancer pain, going all the way back to Portenoy's 1986 article,²⁷⁹ was never more than "weak." Such "weak evidence" was never sufficient to justify the Pharmaceutical Opioid Industry's misleading messaging or the significant increase in opioid prescribing for chronic pain. Moreover, the "weak evidence" based on flawed studies of the past has been refuted by strong, gold-standard randomized clinical trial evidence²⁸⁰ that opioids are *not* more effective than non-opioid pain relievers, while imposing greater risk.²⁸¹ "Weak evidence" of benefit to a small minority of patients was never sufficient to offset the strong evidence of risk. According to the National Academy of Science, Engineering, and Medicine (NASEM) 2017 Report, "Pain Management and the Opioid Epidemic," there is a "*lack of evidence that the drugs are effective for long-term pain management*" (VonKorff *et al.*, 2011) (emphasis added).²⁸²
- k. Evidence of the imbalance between significant risk and minimal benefit is reinforced by the studies demonstrating that significant numbers of pain patients will go on to long-term use of these addictive drugs, even with brief opioid exposure. Long-term exposure increases the risk of developing the disease of opioid addiction.
- l. The ASPPH Report concluded, "We urge that, consistent with CDC guidelines, opioid pain relievers be treated as highly addictive, controlled substances *not typically indicated for long-term use for chronic pain*

²⁷⁸ Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: Systematic analytic review. *Osteoarthr Cartil.* 2016. doi:10.1016/j.joca.2016.01.135, at p. 962.

²⁷⁹ Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 Cases. *Pain.* 1986;25(2):171-186.

²⁸⁰ Krebs *et al.*, "Effect of Opioid," fn. 265, above, at p. 873; Welsch *et al.*, "Opioids in Noncancer Pain," fn. 277, above, at p. 3.

²⁸¹ Krebs *et al.*, "Effect of Opioid," fn. 265, above, at p. 880.

²⁸² NASEM 2017 Report at fn. 42, above p. 29.

outside of active cancer treatment, palliative care, and end-of-life care; and for which lobbying and marketing are inappropriate.”²⁸³

- m. A recent VA/DoD guideline is even more emphatic, stating, “We recommend *against* initiation of long-term opioid therapy for chronic pain. (Strong against).”²⁸⁴ The authors stress that “Based on the evidence, it was considered that *opioid therapy should no longer be given when all nonopioid approaches fail due to the substantial risk of harms*. The CDC guideline states, ‘Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patients.’ Our guideline takes a *stronger stance against opioid therapy*, largely driven by the risk for development of opioid use disorder. Both guidelines find little evidence of benefit for long-term opioid use.”²⁸⁵
- n. I have reviewed a letter submitted by the American Medical Association to the CDC on June 16, 2020, advocating major revisions to the CDC 2016 Guidelines for opioid use.²⁸⁶ While this letter asserts that some patients are benefitting from long-term opioid therapy for chronic pain, it provides no data to support that assertion, nor to rebut the great weight of authority cited above. Further, the letter omitted the undisputed body of

²⁸³ ASPPH Report, “Bringing Science”, fn. 15, above, at p. 11 (emphasis added).

²⁸⁴ Rosenberg JM, et al. Opioid Therapy for Chronic Pain: overview of the 2017 US Department of Veterans Affairs and US Department of Defense clinical practice guidelines. *Pain Medicine*. 2018;19:928-941, at p. 930 (emphasis added).

²⁸⁵ *Id.* (emphasis added)

²⁸⁶ James L. Madara, MD (AMA) to Deborah Dowell, MD (CDC), Re: Docket No. CDC-2020-0029, June 16, 2020, <https://searchlif.ama-assn.org/undefined/documentDownload?uri=%2Funstructured%2Fbinary%2Fletter%2FLETTERS%2F2020-6-16-Letter-to-Dowell-re-Opioid-Rx-Guideline.pdf>. The West Virginia Coalition on Chronic Pain Management, established by the passage of SB 339, issued a series of reports and recommendations in 2019. SB 339 appears to be part of a backlash in response to the CDC Guidelines of 2016. The Coalition found and recommended that West Virginia SB 273 “has inadvertently and inappropriately interfered with the patient practitioner relationship, unnecessarily regulating the evidence-based practice of medicine and, in some cases, even dissuade [sic] physicians who deliver safe, legal, and necessary medical care to patients suffering from pain.” To the extent that this statement refers to the use of opioids for chronic pain, I disagree that encouraging physician freedom is “evidence-based.” To the contrary, as noted elsewhere in this Report, there is substantial evidence that opioids increase the risk of mortality, nonfatal overdose, OUD, and NAS, while there is no reliable evidence of benefit in the treatment of chronic pain with opioids, compared to nonopioid therapies. See Coalition on Chronic Pain Management 2019 Report to the Legislature, West Virginia Legislature.

evidence of OUD and mortality, which would be exacerbated by the absence of the CDC and VA/DoD guidelines to limit dose and duration of opioid therapy. I agree with the AMA letter's advocacy for a preference for non-pharmacologic and non-opioid therapies; however, the evidence supports the VA/DoD determination that opioids should no longer be given even when other approaches fail, due to the substantial risk of harms. Physicians' freedom to treat their patients as they choose is not absolute, but must be tempered by evidence and data. AMA's emphasis on physicians' freedom is out of proportion to the clear evidence of risk, and the lack of evidence of benefit, for long-term opioid therapy for chronic pain.

- o. Opioids have been generally considered appropriate for cancer pain, because cancer treatment has been closely aligned with end-of-life care, a stage when risks of addiction are considered less important than potential palliative care. However, patients with cancer related pain, even at the end of life, are not immune to addiction and they should be monitored carefully for addiction and other adverse consequences, and should receive the lowest dose for the shortest possible duration.
 - i. A first-person perspective piece in the *New England Journal of Medicine*, describes the experience of an oncologist (cancer doctor) whose patient gets addicted to opioids.²⁸⁷ In my clinical experience, opioid misuse and addiction are as common among cancer patients as non-cancer patients.
 - ii. There were more than 15 million cancer survivors in the United States in 2016.²⁸⁸ Even patients with cancers once considered incurable, now go into remission for decades and more, emphasizing the need for caution in treating a very large population of patients with opioids.

7. The Pharmaceutical Opioid Industry misrepresented that the risk of addiction to prescription opioids is “rare,” or “less than 1%,” when in fact prescription opioids are as addictive as heroin, and the risk of addiction is far higher than stated by

²⁸⁷ Loren AW. Harder to Treat Than Leukemia - Opioid Use Disorder in Survivors of Cancer. *NEJM*. 2018;379(26).

²⁸⁸ Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the “silver tsunami”: Prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev*. 2016. doi:10.1158/1055-9965.EPI-16-0133, at p. 1029.

the Industry. The best, conservative data show an opioid addiction prevalence of 10-30% among chronic pain patients prescribed opioids.

- a. Even when being prescribed by a doctor for a legitimate pain condition, opioid painkillers are as addictive as heroin purchased on a street corner, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain.²⁸⁹ The addictiveness of prescription opioids has been demonstrated in many studies, yet the Pharmaceutical Opioid Industry has consistently downplayed this risk.
- b. A 2015 systematic review by Vowles, *et al.*, provides the most reliable pooled estimate of the risk of addiction (10-30%) in patients receiving chronic opioid therapy.²⁹⁰ The Vowles review is cited by the ASPPH Task Force to state the risk of addiction and misuse of prescription opioids,²⁹¹ reinforcing my opinion as to the validity of the Vowles review.
 - i. Vowles' data synthesis prioritized studies using real world data designed to research opioid misuse and addiction. They also prioritized subjects from real world populations, rather than pre-screened clinical trial subjects enrolled in studies not designed to assess misuse or addiction. The authors adopted *a priori* criteria to assess study quality, and then checked their pooled results against the data from the highest quality studies.²⁹² (By contrast, Fishbain *et al.*, described below, completely excluded studies that did not meet their quality standards, which they admitted were arbitrary.) Further, Vowles, *et al.* disclosed that they had no conflicts of interest.²⁹³ Because most available studies used patient questionnaires rather than objective urine drug screening, Vowles'

²⁸⁹ See, e.g., Okie S, A flood of opioids, a rising tide of deaths. *NEJM* 2010;363(21): 1981-1985: Prescription opioids are “essentially legal heroin.” (Quoting FDA Advisory Committee member Lewis Nelson. “We need to think about how we would conduct a REMS [Risk Evaluation and Mitigation Strategy] if we were going to be marketing heroin.” *Id.* at 1981.)

²⁹⁰ Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, Van Der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain*. 2015.

doi:10.1097/01.j.pain.0000460357.01998.f1. at p. 569. I address the link between prescription opioid addiction and heroin addiction below in paragraph C.8.g.

²⁹¹ ASPPH Report, “Bringing Science”, fn. 15, above, at p. 14.

²⁹² Vowles, “Rates of Opioid Misuse”, fn. 290, above, at p. 570-571.

²⁹³ *Id.* at p. 575.

analysis would represent a likely underestimate of addiction, despite a more appropriate selection of real world populations for the study.

- ii. In their systematic review and meta-analysis from 38 studies, Vowles, *et al.* cite a wide range of problematic prescription opioid use in patients being treated for a medical condition, ranging from <1% to 81% across studies. Across most calculations, rates of opioid misuse averaged between 21% and 29% (range, 95% confidence interval [CI]: 13%-38%), and rates of opioid addiction averaged between 8% and 12% (range, 95% CI: 3%-17%).²⁹⁴
- iii. Even the lower risk classification of 8-12% would be considered a “very common” risk according to the World Health Organization and the Council of International Organizations of Medical Sciences:²⁹⁵
 - A. Very common $\geq 1/10$
 - B. Common $\geq 1/100 >$ and $< 1/10$
 - C. Uncommon $\geq 1/1000$ and $< 1/100$
 - D. Rare $\geq 1/10,000$ and $< 1/1,000$
 - E. Very rare $< 1/10,000$
 - F. Although the US has not adopted a standard hierarchy like WHO/CIOMS, frequency of adverse events in product information material in the United States is consistent with the WHO standards: “rare” in US labels is commonly <

²⁹⁴ *Id.* at, pp. 572-573. It is noteworthy that well-respected scientific sources have cited Vowles’ article as a reliable estimate of risk. See, e.g., Els, *et al.*, High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2017 Oct; 2017(10): CD012299, citing the Vowles article as support for “rates of addiction averaging between 8% and 12%.

²⁹⁵ World Health Organization, CIOMS, http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf, at p. 10.

1/1000; “Infrequent” is >1/1,000 to < 1/100; and anything over 1/100 is “frequent.”²⁹⁶

- iv. Vowles’ definition of “misuse” as culled from the included articles is consistent with the DSM-5 definition of mild opioid use disorder.²⁹⁷ As such, the prevalence of opioid use disorder in Vowles’ review using DSM-5 criteria is between 21-29%, including the spectrum from mild through severe OUD.²⁹⁸ (This is reasonably consistent with the Boscarino, *et al.* study²⁹⁹ described below.)
- v. As with other meta-analyses, reports of misuse/addiction were higher in studies which relied on urine drug testing instead of self-report. For example, included in the Vowles analysis, a study by Brown, *et al.* demonstrated the lower rates based on self-report versus those based on urine toxicology.³⁰⁰
 - A. This was a nonrandomized, open-label study of morphine sulfate ER (Avinza) for a titration period of 2-4 weeks followed by treatment for 12 weeks, administered to patients in primary care settings, evaluated for risk stratification and aberrant behaviors (including urine screening, early renewal requests, increased dose without authorization, oversedation).³⁰¹
 - B. Only 561 (38%) of the 1,570 originally enrolled patients completed the study, despite its relatively brief duration of

²⁹⁶ Eriksson R, Aagaard L, Jensen LJ, *et al.* Discrepancies in listed adverse drug reactions in pharmaceutical product information supplied by the regulatory authorities in Denmark and the USA. *Pharmacol Res Perspect.* 2014;2(3):1-10. doi:10.1002/prp2.38, at p. 6.

²⁹⁷ Vowles, “Rates of Opioid Misuse”, fn. 290, above, at p. 574.

²⁹⁸ *Id.* at p. 569.

²⁹⁹ Boscarino J, Rukstalis MR, Hoffman SN, *et al.* Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *J Addict Dis.* 2011;30(3):185-194. doi:10.1080/10550887.2011.581961.

³⁰⁰ Brown J, Setnik B, Lee K, *et al.* Assessment, stratification, and monitoring of the risk for prescription opioid misuse and abuse in the primary care setting. *J. Opioid Management.* 2011;(December):467-483 doi:10.5055/jom.2011.0088.

³⁰¹ *Id.* at p. 468.

12 weeks of treatment. Of the 890 patients for whom reasons for withdrawal were provided, 410 (46%) included adverse events or failure of treatment among their reasons to withdraw. Five percent were asked to withdraw due to investigator assessment of “high risk level for drug abuse/misuse” after enrollment, and another 5% for “noncompliance.”³⁰²

- C. The Vowles analysis incorporates the Brown study’s assertion that 2-3% of patients exhibited aberrant drug-related behaviors during visits 2 through 4, and 6% at visit 5, listing those percentages in the “misuse” column.³⁰³
- D. However, Urine Drug Screening (UDS) showed much higher rates of misuse and/or addictive use (although Vowles did not include these findings in the analysis): In particular, 17, 11, 11 and 15 subjects had positive UDS for oxycodone in weeks 2-5, despite prohibition of that drug after Visit 1.³⁰⁴ By week 5, there were 79 subjects remaining in the study, and the 15 subjects with positive UDS for oxycodone yield a rate of 19% misuse and/or addictive use. This finding provides objective evidence that the prevalence of aberrant drug-related behavior was approximately 3 to 9 times the “2-6%” rate of aberrant drug related behaviors reported by the investigators³⁰⁵ and cited by Vowles. Such use occurred despite patients having signed agreements to refrain from illicit drug use, and despite knowledge that UDS would be conducted.³⁰⁶
- E. Objective measures of addictive/aberrant behavior like drug screening results are more reliable than questionnaire responses, and these data from the Brown study support that view.

³⁰² *Id.* at p. 473.

³⁰³ *Id.* at p. 572.

³⁰⁴ *Id.* at p. 475, Figure 2.

³⁰⁵ *Id.* at p. 476.

³⁰⁶ *Id.* at pp. 478-479.

- F. This study was Pfizer-sponsored. Authors included Pfizer/subsidiaries/consultants.³⁰⁷
- vi. Also included in the Vowles analysis was a study by Fleming, *et al.*, again highlighting the discrepancy between self-report and urine toxicology.³⁰⁸
 - A. This Fleming article reported on substance use disorders among 801 chronic pain patients receiving daily opioid therapy from the same Wisconsin primary care practices that provided the population analyzed in the Fleming article discussed above. Fleming reported a point prevalence of 3.8% for opioid use disorder and 9.7% for substance abuse and/or dependence, using DSM-4 criteria³⁰⁹ and Vowles incorporated these percentages into the data synthesis.
 - B. The diagnoses included in the percentages above were based on a 2-hour interview of each patient by the doctor or nurse at the primary care practice.³¹⁰ As referenced above, Fleming noted the large disparity between the patients' self-reporting of other drug use and the results of urine drug screening. There were 156 positive urine screens for cannabis compared to 106 self-reports, and 60 positive urine screens for cocaine compared to 24 self-reports.³¹¹
 - C. Although the article provided urine drug screen data on certain illicit drugs, sufficient to show the discrepancy between deceptive self-report and objective toxicology, the article did not provide data on the results of urine screens specifically for opioids, so there were no data to determine how many patients used opioids that were not prescribed

³⁰⁷ *Id.* at p. 481.

³⁰⁸ Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance Use Disorders in a Primary Care Sample Receiving Daily Opioid Therapy. *J Pain*. 2007. doi:10.1016/j.jpaa.2012.02.008, at p. 579.

³⁰⁹ *Id.* at p. 573.

³¹⁰ *Id.* at p. 574.

³¹¹ *Id.* at p. 579.

- (evidence of misuse), or less/no evidence of the prescribed opioids (evidence of possible diversion).
- D. Fleming also reported that “the frequency of opioid use disorders was 4 times higher in patients receiving opioid therapy compared with general population samples (3.8% vs 0.9%).”³¹²
 - E. Despite acknowledging the disparity between toxicology tests and diagnoses based on interview data, Fleming concluded that the “3.8% rate of opioid addiction is a small risk compared with the alternative of continuous pain and suffering. The data presented in this paper support the use of opioids for the treatment of chronic pain by primary care physicians.”³¹³ I disagree with this interpretation of the findings, especially in light of (a) the acknowledged disparity between the urine drug screen rate and the rate based on self-reports; (b) the unreliability of the latter; and (c) the unwarranted assumption that opioid therapy would alleviate chronic pain and suffering as a trade-off for accepting the risk of dependence or addiction.
 - c. A study indicating a high risk of addiction from prescription opioids was published by Boscarino, *et al.*, who analyzed addiction rates in a large population of patients receiving opioids to treat a medical condition, and found a 41.3% lifetime prevalence of opioid use disorder (using DSM-5 criteria).³¹⁴ The research in this study is strengthened by the fact that it was based on a random sample of outpatients seen in a large multispecialty group practice. Subjects were identified through drug orders in the electronic health records and subsequently were interviewed using the final DSM-5 criteria. Weaknesses include the low numbers willing to be interviewed (33%).³¹⁵

³¹² Fleming, *et al.*, “Substance Use Disorders,” fn. 308, above, at p. 573.

³¹³ *Id.* at p. 581.

³¹⁴ Boscarino J, Hoffman S, Han J. Opioid-use disorder among patients on long-term opioid therapy: impact of final DSM-5 diagnostic criteria on prevalence and correlates. *Subst. Abuse Rehabil.* 2015:83. doi:10.2147/SAR.S85667, at p. 83.

³¹⁵ *Id.* at p. 84.

- i. “Using electronic records from a large US health care system, we identified outpatients receiving five or more prescription orders for opioid therapy in the past 12 months for noncancer pain (mean prescription orders =10.72; standard deviation =4.96). In 2008, we completed diagnostic interviews with 705 of these patients using the DSM-4 criteria. In the current study, we reassessed these results using the final DSM-5 criteria. Results: The lifetime prevalence of DSM-5 opioid-use disorders using the final DSM-5 criteria was 58.7% for no or few symptoms (< 2), 28.1% for mild symptoms (2–3), 9.7% for moderate symptoms (4–5), and 3.5% for severe symptoms (six or more). Thus, the lifetime prevalence of “any” prescription opioid-use disorder in this cohort was 41.3% (95% confidence interval [CI] =37.6–45.0).”³¹⁶
- ii. “A comparison to the DSM-4 criteria indicated that the majority of patients with lifetime DSM-4 opioid dependence were now classified as having mild opioid-use disorder, based on the DSM-5 criteria (53.6%; 95% CI =44.1–62.8). In ordinal logistic regression predicting no/few, mild, moderate, and severe opioid-use disorder, the best predictors were age 65 years, current pain impairment, trouble sleeping, suicidal thoughts, anxiety disorders, illicit drug use, and history of substance abuse treatment.”³¹⁷
- iii. In my opinion, the moderate-severe categories of DSM-5 OUD are consistent with Vowles’ definitions of addiction, and the milder DSM-5 diagnoses are more consistent with Vowles’ definition of misuse.³¹⁸ Accordingly, the totals of 13% “moderate to severe opioid use disorder” in Boscarino are consistent with Vowles’ findings of 8-12% “addicted”; further, Vowles’ finding of 21-29% “misuse” is reasonably consistent with Boscarino’s report of 28% with “mild opioid use disorder.” In other words, both of these publications are reasonably consistent in assessing the risk of opioid addiction, ranging from mild to severe, in a clinical population of patients receiving opioids.

³¹⁶ *Id.* at p. 83.

³¹⁷ *Id.* at p. 83.

³¹⁸ Vowles, “Rates of Opioid Misuse”, fn. 290, above, at p. 574.

- d. Even very limited exposure to prescription opioids can result in addiction, as evidenced by a study in teens and young adults: 14,888 persons aged 16 to 25 years-old who received an initial opioid prescription from a dentist, found that 6% were diagnosed with an opioid use disorder (OUD) within one year. For women in this group, the rate was 10%. This study highlights the risk to teens and young adults, even after limited exposure to a dental procedure, such as removal of wisdom teeth.³¹⁹
- e. A 2019 study found that for opioid-naïve individuals receiving an initial opioid prescription between 2011-2014, “long-term opioid use (3+ months) is associated with more than double the risk of incident OUD and opioid-related death.”³²⁰ In fact, the cumulative incidence of opioid use disorder rose for each time period measured after opioid naïve individuals received an opioid prescription, so that for those receiving an initial opioid prescription in 2011, the cumulative incidence of OUD was 0.62% at 6 months, 1.18% at 1 year, 2.244% at 2 years, 3.79% at 3 years and 4.90% at 4 years.³²¹
- f. Numerous other publications have reported addiction rates from prescription opioids higher than those that appear in the Pharmaceutical Opioid Industry promotional materials that I have reviewed. These include the following prevalence studies cited in the Vowles³²² data synthesis: Manchikanti (2003),³²³ Cowan (2003),³²⁴ Adams (2006),³²⁵ Fleming (2007),³²⁶ Banta-Green (2009),³²⁷ Schneider (2009),³²⁸ Edlund (2007),³²⁹

³¹⁹ Schroeder AR, Dehghan M, Newman TB, Bentley JP, Park KT. Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and Abuse. *JAMA Intern Med.* 2018, at p. E6.

³²⁰ Burke LG, et al. Trends in opioid use disorder and overdose among opioid-naïve individuals receiving an opioid prescription in Massachusetts from 2011 to 2014. *Addiction.* 2019;1-12, at p. 9

³²¹ *Id.*, p. 6, Table 3

³²² Vowles, *et al.*, “Rates of Opioid Misuse,” fn. 290, above.

³²³ Manchikanti *et.al* Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. *J Ky Med Assoc* 2003;101:511-17, at p. 511.

³²⁴ Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. *Pain Med.* 2003;4(4):340-351, at p. 340.

³²⁵ Adams EH, Breiner S, Cicero TJ, *et al.* A Comparison of the Abuse Liability of Tramadol, NSAIDs, and Hydrocodone in Patients with Chronic Pain. *J Pain Symptom Manage.* 2006;31(5):465-476, at p. 465.

³²⁶ Fleming, *et al.*, “Substance Use Disorders,” fn.308, above, at p. 573.

Hojsted (2010),³³⁰ Jamison (2010),³³¹ Passik (2011),³³² and Meltzer (2012),³³³ which reported addiction at 8.4%, 2.8%, 4.9%, 3.8%, 13%, 15.7%, 0.7%, 14.4-19.3%, 34.1%, 6-11%, and 23%, respectively. With one exception, all of these studies showed addiction prevalence multiple times higher than the “less than one percent” figure that Defendants continued to cite, while omitting data from these peer-reviewed studies of relevant, real world populations of chronic opioid patients.³³⁴

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³²⁷ Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn D a. Opioid use behaviors, mental health and pain--development of a typology of chronic pain patients. *Drug Alcohol Depend.* 2009;104(1-2):34-42, at p. 37.

³²⁸ Schneider, MD, PhD JP, Kirsh, PhD KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: A quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. *J Opioid Manag.* 2010;6(6):385-395, at p. 390.

³²⁹ Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? *Pain Med.* 2007. doi:10.1111/j.1526-4637.2006.00200.x, at p. 651.

³³⁰ Højsted J, Nielsen PR, Guldstrand SK, Frich L, Sjøgren P. Classification and identification of opioid addiction in chronic pain patients. *Eur J Pain.* 2010;14(10):1014-1020, at p. 1014.

³³¹ Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender Differences in Risk Factors for Aberrant Prescription Opioid Use. *J Pain.* 2010. doi:10.1016/j.jpain.2009.07.016, at p. 5.

³³² Passik SD, Messina J, Golsorkhi A, Xie F. Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. *J Pain Symptom Manage.* 2011;41(1):116-125, at p. 116.

³³³ Meltzer, E, Rybin, D, et al. Aberrant Drug-Related Behaviors: Unsystematic Documentation Does Not Identify Prescription Drug Use Disorder. *Pain Med.* 2012 November; 13(11): 1436-1443, at p. 1437.

³³⁴ The sole exception, the Edlund (2007) study, can be explained in that the 0.7% incidence pertained to the entire healthcare database, rather than the subset of prescription opioid users. As to the latter group, the incidence of addiction was actually 7.3%, which is consistent with the other data synthesized by Vowles. Edlund, et al., “Do Users Have Higher Rates,” fn. 329, above, at p. 651. Because this distinction is important and not obvious, I provide the additional details below.

First, the data used in the Edlund 2007 study came from a nationally representative community sample, Healthcare for Communities (HCC). The sample consisted of 9,279 people who were interviewed to investigate self-reported opioid misuse and “problem” opioid misuse among users and non-users of prescribed opioids, as well as use/ “problem use” of other substances (illicit drugs other than opioids, alcohol). “Opioid misuse” was defined to mean either without a doctor’s prescription, or in a larger amount or for a longer time than prescribed. “Problem opioid use” added criteria of tolerance and/or psychological or emotional problems due to drug use to the general “misuse” definition. *Id.* at pp. 649-650.

This Edlund study did not provide any data on “addiction.” Nevertheless, the Vowles data synthesis included a value of 0.7% for “addiction.” Vowles, et al., “Rates of Opioid Misuse,” fn. 290, above, at p. 572, Table 2. However, the Edlund definition of “problem opioid use” is consistent with Vowles’ definition of “addiction” to

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- g. The above-described studies show that pain treatment with opioids is naturally linked with addiction. Furthermore, this linkage would have been known and obvious to Defendants before and throughout the period of time when they marketed and promoted their opioid medications with the false message that addiction was “less than 1%,” or “rare,” or “uncommon,” and that false message deprived doctors and patients of necessary data to inform the true risks of chronic opioid therapy. Internal documents show that Defendants were aware of the link between prescription opioids and opioid misuse, diversion, addiction and death, as discussed below.
- i. On April 22, 2011, Joseph Tomkiewicz, Corporate Investigator at AmerisourceBergen, sent an email to colleagues under the subject “Saw This and Had To Share It ...”³³⁵ It was a parody written to the tune of the Beverly Hillbillies: “Come and listen to a story about a man named Jed, A poor mountaineer, barely kept his habit fed.... Said Sunny Florida is the place you ought to be, So they loaded up the truck and drove speedily, South, that is, Pain Clinics, cash ‘n carry, A Bevy of Pillbillies Pill Mills that is. Buy some

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mean a “[p]attern of continued use with experience of, or demonstrated potential for, harm, (e.g., impaired control over drug use, compulsive use, continued use despite harm, and craving).” *Id.* at p. 570.

Further, the reference to “0.7%” in the Edlund 2007 article appearing at p. 651, stated the percentage of problem opioid misuse in “*the total HCC sample*,” (emphasis added), which consisted of 8,997 (97%) nonusers of prescription opioids compared to 282 (3%) of the HCC sample who were prescription opioid users. The Edlund study reported, “Rates of problem opioid misuse were *significantly higher in those with prescription opioid use* (7.3%, 17 out of 282, vs. 0.5%, 69 out of 8,997, P<0.001.”; (emphasis added)). Edlund, *et al.*, “Do Users Have Higher Rates,” fn. 329, above, at p. 651.

In the absence of any data specific to addiction in the Edlund article, it can only be inferred that Vowles intended to use Edlund’s “problem opioid misuse” as a surrogate for addiction, and that the reference to 0.7% for the total population is inappropriate, since all of the other studies that Vowles synthesized had determined the percentage of addiction/ misuse among subjects exposed to prescription opioids, and not the percentage of addiction/misuse among a general population consisting almost entirely of non-users of prescription opioids.

Thus, the proper figure from the Edlund study to include in the Vowles data synthesis would have been “7.3%, 17 out of 282” prescription opioid users, and the inclusion of the prescription opioid nonusers differentiates the Edlund study from all others that Vowles used in his data synthesis. At 7.3%, the Edlund study is very similar to the range of 8-12% addiction that Vowles assessed for the studies as a whole.

Finally, Edlund acknowledged, “Our analyses of substance abuse rely on self-report, which might suffer from recall bias, or respondents might under-report symptoms due to the stigma associated with illicit substance abuse. To the extent this is true, our results are underestimates of the true rates.” *Id.* at p. 654. Accordingly, 7.3% is a lower bound, and the true rate of addiction among the population in the Edlund study may well have been greater.
³³⁵ ABDCMDL05795672

pills. Take a load home.”³³⁶ This is shocking for its gross disregard of human suffering caused by the opioid epidemic. Just as shocking is the fact that the offensive email was circulated among several high-ranking regulatory affairs executives and diversion control investigators at Amerisource Bergen, who not only failed to express disapproval, but rather stated, “I sent this to you a month or so ago--nice to see it recirculated,” with a “smiley face icon.”³³⁷

- ii. On July 2, 2012, the same AmerisourceBergen employee, Joseph Tomkiewicz, also sent to colleagues under the subject “Oxycontin for kids”, an image resembling a Kellogg’s cereal box, but instead of “Kellogg’s” it reads “Killogg’s”, the cereal is called “SMACK”, a slang term for heroin, and the cereal box features a frog with a syringe getting ready to inject, holding up a spoonful of pills, next to a bowl of coupons labeled “Free Trial Offer.”³³⁸ This image encapsulates the link between prescription opioids, industry promotion of those opioids through marketing strategies like coupons for free samples, and the development of opioid addiction which in some cases leads to illicit opioids like heroin. As in the case of the “Pillbillies” email, the “Smack” email was circulated among several employees without evidence of any objections.³³⁹
- iii. On June 19, 2015, a memorandum from Healthcare Distribution Management Association (HDMA) titled “Strategy to Turn the

³³⁶ *Id.*

³³⁷ *Id.* The email’s recipients included Julie Eddy (Director State Government Affairs) Chris Zimmerman (Vice President Corporate Security and Regulatory Affairs), Edward Hazewski (Director Diversion Control Program) , Kevin Kreutzer (Diversion Control Investigator), David Breitmayer (Diversion Control Investigator), Paul Ross (Senior Director Corporate Security Regulatory Affairs), Bruce Gundy (Director of Investigations) , Robert Crow (Director Security Services), and Steve Mays (Senior Director Corporate Security and Regulatory Affairs - Group Compliance Officer, Drug Distribution). See <https://www.linkedin.com/in/julie-eddy-458b118>, <https://www.linkedin.com/in/chriszimmerman>, <https://www.linkedin.com/in/edwardhazewski>, <https://www.linkedin.com/in/kevin-kreutzer-b1763512>, <https://www.linkedin.com/in/davebreitmayer>, ABDCMDL05775790, <https://www.linkedin.com/in/bruce-gundy-5b5085a>, <https://www.linkedin.com/in/robert-crow-7b97aa192>, <https://www.linkedin.com/in/steve-mays-4783336>.

³³⁸ ABDCMDL00532594

³³⁹ *Id.* The email’s recipients included Kevin Kreutzer (Diversion Control Investigator), David Breitmayer (Diversion Control Investigator), Edward Hazewski (Director Diversion Control Program), and Elizabeth Garcia (Corporate Investigator). See <https://www.linkedin.com/in/kevin-kreutzer-b1763512>, <https://www.linkedin.com/in/davebreitmayer>, <https://www.linkedin.com/in/edwardhazewski>, ABDCMDL00532649.

Tide in West Virginia,” summarizes suggestions for distributors to fend off negative press and lawsuits due to their role in inciting the opioid epidemic.³⁴⁰ This memorandum includes the statement, “The fact is that 200 million pills over a four-year period is a significant problem. The story is made worse given the following: The distributors do not want to make their sales data public.... While patient access issues can help support the need for distributors, they can also turn against distributors, as these companies must self-monitor and restrict the supply of medicine to protect their ability to continue serving the needs of doctors, pharmacists, and their patients.”³⁴¹ HDMA is an alliance of pharmaceutical distributors, largely funded by the Defendants in this litigation.³⁴²

- iv. In 2001, Janssen convened an advisory board to discuss Janssen’s Duragesic patch. When the topic of Duragesic’s addictive potential was raised, advisory board members, who were all KOLs in the field of pain, had this to say:
 - A. “All opioids are in the same class and have the same potential for abuse.”³⁴³
 - B. “So why is OxyContin so subject to abuse? ... Availability - \$1B worth on the market. Street price indicates likelihood of diversion.”³⁴⁴
 - C. “Drug abusers will figure out how to abuse Duragesic once it is more available As market share goes up, so will abuse. Over-promising on the lack of abuseability is what got OxyContin in trouble. Duragesic should not repeat the same mistake.”³⁴⁵

³⁴⁰ ABDCMDL00269293

³⁴¹ *Id.*

³⁴² Healthcare Distribution Alliance (formerly known as the HDMA) leadership remains with David Neu of Amerisource, <https://www.hda.org/persons/david-neu>

³⁴³ JAN-MS-00481055 at 1059.

³⁴⁴ *Id.*

³⁴⁵ *Id.* at 1060.

- D. These comments make it clear that members of the advisory board were well aware of the risks of misuse, addiction, and overdose deaths caused by prescription opioids, and that these risks were directly tied to availability, which increases the risk of patients getting addicted, and also diversion to non-patients. Despite the KOLs advice, Janssen promoted Duragesic in ways similar to those that “got OxyContin in trouble,”³⁴⁶ including free samples and aggressive marketing of purported low risk of addiction (See 5.a.ii for discussion of Duragesic free samples and promotion) .

- h. Opioid manufacturers have sought to counter evidence of addiction risk by claiming ‘abuse-deterrant’ status for their products. For example, Janssen sought FDA approval of an “abuse deterrence” claim for tapentadol (Nucynta). However, an FDA Memorandum in 2008 noted that tapentadol displayed “high abuse potential comparable to that of hydromorphone, a drug that is associated with high levels of abuse.”³⁴⁷ The FDA authors likened tapentadol to “other strong opioids such as hydromorphone and oxycodone,” and warned against using tapentadol IR “chronically as this increases the adverse event profile, including the likelihood of addiction and abuse.”³⁴⁸ Further, the memorandum noted that tapentadol causes dependence and subjective withdrawal on par with oxycodone.³⁴⁹

- i. A study by Butler *et al.* in *Pain Medicine* (2015), sponsored by Janssen, reports on a population of about 114,000 patients evaluated for prevalence and prescription-adjusted prevalence of self-reported, past 30-day “abuse” of tapentadol in comparison to

³⁴⁶ *Id.*

³⁴⁷ Food and Drug Administration Center for Drug Evaluation and Research (FDA-CDER), Application Number: 22-304 (November 4, 2008), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_OtherR.pdf, at p. 2. The relatively lower rates of misuse and diversion of tapentadol formulations in the community to date are likely a function of lower prescribing rates, a shorter period since the drug was approved for sale, and lower level awareness of the drug among prescribers, patient consumers, and individuals with opioid addiction, not an intrinsically lower abuse potential of tapentadol.

³⁴⁸ *Id.* at p. 3.

³⁴⁹ *Id.* at p. 9.

several other opioids, between January 2011 and September 2012.³⁵⁰ Tapentadol IR “abuse” prevalence was reported to be lower than all other opioids except fentanyl, while tapentadol ER “abuse” prevalence was reported to be lower than other opioids except hydromorphone.³⁵¹ (Of interest, 20.8% of the population self-reported “abuse” of analgesics within the last 30 days.)³⁵² Most importantly, rate of “abuse” adjusted for number of prescriptions³⁵³ (tapentadol had far fewer prescriptions than other opioids), demonstrates that tapentadol “abuse” was greater than tramadol and nearly identical to hydrocodone. It is likely that tapentadol, with a similar “abuse potential” to hydrocodone, would show similar rates of addiction and diversion if prescribed at equal volumes.

- ii. A study by Cepeda *et al.* (2013), also Janssen-funded, reported a 65% lower rate of “abuse” in a relatively small cohort of 6,000 total tapentadol subjects compared to 37,000 oxycodone subjects, identified in 2010 and followed for one year.³⁵⁴ However, the study provided no details as to the duration of exposure to either drug. Since duration of exposure is a significant cause of opioid use disorder, the absence of such data weakens the validity of the findings. Also, there are significant differences in prescribing rates between tapentadol and oxycodone, with much higher prescribing for oxycodone. Comparing these two drugs fails to take into account the longer history on the market and greater drug awareness for oxycodone. This is further supported by the animal and human studies finding tapentadol comparable to morphine, hydromorphone, and oxycodone in its likeability, reinforcing properties, and propensity for physiologic dependence, as noted in the 2008 FDA memorandum referenced above.³⁵⁵

³⁵⁰ Butler SF *et al.* Tapentadol Abuse Potential: a postmarketing evaluation using a sample of individuals evaluated for substance abuse treatment. *Pain Medicine*. 2015;16: 119-130, at p. 119.

³⁵¹ *Id.*

³⁵² *Id.* at p. 122.

³⁵³ *Id.* at p. 119.

³⁵⁴ Cepeda, MS *et al.* Comparison of the risks of opioid abuse or dependence between tapentadol and oxycodone: results from a cohort study. *Journal of Pain*. 2013;14(10): 1227-1241 at p. 1227.

³⁵⁵ FDA-CDER. fn. 347, above, at pp. 8-10.

- iii. For the same reasons, a drug diversion surveillance study by Dart *et al.*, which finds relatively low rates of tapentadol diversion, is not a good measure of problematic opioid use in the community.³⁵⁶ Lower rates of tapentadol diversion are likely attributable to lower tapentadol prescribing rates and the ready availability of other opioids in the community. This opinion is supported by FDA reviewers, who stated in a 2013 letter to Janssen that in regard to tapentadol “abuse” in the community, “it is unclear whether the relatively low amount of abuse detected is due to a low level of awareness of the drug as a consequence of its short marketing history, low utilization, reduced opioid receptor affinity of the tapentadol molecule, or the tamper-resistant characteristics of the extended-release formulation.”³⁵⁷
- i. Tramadol is an addictive opioid yet was marketed as a “non-narcotic.”
 - i. After ingestion, tramadol is metabolized by the cytochrome P450 2D6 liver enzyme into an active metabolite that binds the opioid receptors and exhibits the same properties as other opioids, like morphine. J&J was well aware of tramadol’s opioid status before marketing it to the public and was specifically instructed not to market tramadol as non-scheduled, i.e. non-addictive, given its robust activity at the opioid receptor.³⁵⁸ Despite knowledge of tramadol’s potent activity at the opioid receptor, and despite a direct warning from the FDA, as shown below J&J falsely marketed tramadol as “non-narcotic” and repeatedly called attention to its unscheduled status, thus misleading prescribers into thinking tramadol is safer than other opioids and carries less risk of addiction.
 - ii. The 1995 tramadol New Drug Application (NDA) makes it clear that manufacturers knew from before tramadol was marketed that the mechanism of action is that of an opioid. The original labeling for ULTRAM (tramadol) stated, “ULTRAM’s opioid activity

³⁵⁶ Dart RC, *et al.* Assessment of the abuse of tapentadol immediate release: the first 24 months. *Journal of Opioid Management* 2012; 8:395-402.

³⁵⁷ FDA-CDER Letter to Janssen (August 1, 2003). JAN-MS-00704213 at 4219.

³⁵⁸ FDA-CDER. NDA 20-281 File. (March 3, 1995).

https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020281Orig1s000rev.pdf..

derives from low affinity binding of the parent compound to u-opioid receptors and higher affinity binding of the M-1 metabolite....,” and the NDA Review of PharmacologyToxicology Data stated, “This metabolite [M1] appears to play a major role in the opioid binding and analgesic effects, 4 times to nearly 200 times as potent as the parent tramadol and is often present at equivalent blood levels.”³⁵⁹

- iii. In a letter from the FDA to the manufacturers dated March 3, 1995, manufacturers were warned not to call attention to tramadol’s (Ultram’s) status as a non-scheduled, i.e. non-addictive drug: “As Ultram may have an abuse potential of an unknown degree, you are not permitted to advertise, promote or market the drug product by calling attention to its unscheduled status under the U.S. Controlled Substance Act.”³⁶⁰
- iv. In a 2008 internal J&J document, under “Strengths (Prioritized)”, is the statement: “Ultram ER [tramadol extended release] is non-narcotic which mid-level practitioners can prescribe.”³⁶¹ The reference to mid-level practitioners implies that tramadol is safer than ‘narcotics’ i.e. opioids, and hence can be prescribed by nurse practitioners who have less training in the risks of pharmacotherapy.
- v. The “Ultram ER Core Visual Aid Tour” depicts tramadol (Ultram ER) as a safer stepping-stone in a “pain treatment ladder” between non-opioid medications like acetaminophen/NSAIDS and “scheduled narcotics.” See “Key Points – PAIN LADDER: Use ULTRAM ER before moving to scheduled narcotics to treat moderate chronic pain; Around the clock pain deserves around the clock treatment without the concerns of scheduled narcotics.”³⁶² Although it is accurate that tramadol was not scheduled before 2014, this pain treatment ladder is misleading because it suggests that tramadol is not an opioid, and that tramadol is safer than opioids, neither of which is true.

³⁵⁹ *Id.*, at pp. 8, 332.

³⁶⁰ *Id.* at p. 5.

³⁶¹ JAN-TX-00022608, produced natively at *2.

³⁶² JAN-TX-00001492, produced natively at *9.

- vi. Tramadol sales representatives were coached to say the following to prescribers while showing them pictures from a direct-to-consumer television ad for Ultram ER, of people looking healthy and happy while engaged in different physical activities - hiking, playing on the beach, climbing stairs: “Doctor, after seeing this commercial, your patients may come to you asking about treatment options, including those that work around the clock. Those patients with chronic low back or osteoarthritis pain may be especially interested. Let’s discuss such a challenging patient in your practice – maybe you have a 50 year old female with chronic OA pain who needs to treat her pain on a daily basis and isn’t getting sufficient pain relief from her prescription NSAIDs, but whom you would rather not move to a scheduled narcotic. For that patient, why not put her on ULTRAM ER before moving her to a scheduled narcotic?”³⁶³ (“Ultram ER Core Visual Aid Tour”) The suggestion here is that Ultram ER is somehow less risky than other opioids because it was not “scheduled.” There is no evidence to support this suggestion and substantial evidence to the contrary.
- vii. Tramadol is addictive, as demonstrated by the references below.
- viii. In recognition of its addictive potential, in 2014 tramadol was changed from a non-scheduled drug, to a scheduled drug (Schedule IV).³⁶⁴
- ix. A study of treatment-seeking adolescents at a substance use treatment facility in Sweden showed “tramadol was by far the most prevalent opioid detected.”³⁶⁵
- x. A study of long-term use of tramadol following acute exposure, published in the British Medical Journal (BMJ 2019) states: “Our study suggests that tramadol carries a similar or somewhat greater risk of transitioning from acute to prolonged use compared with other short acting opioids. Although prescribing was relatively

³⁶³ *Id.*, at *7

³⁶⁴ Schedules of Controlled Substances: Placement of Tramadol into Schedule IV. 79 Fed. Reg. 37,628 (July 2, 2014).at p. 37628

³⁶⁵ Olsson MO, *et al.* High rates of tramadol use among treatment-seeking adolescents in Malmo, Sweden: a study of hair analysis of nonmedical prescription opioid use. *Journal of Addiction* 2015:1-9, at p. 1.

infrequent (4% of patients with opioid fills, including those who received tramadol with other short acting opioids), tramadol was the third most frequently prescribed opioid in this study (after hydrocodone and short acting oxycodone), and its use seems to be increasing (fig 1).³⁶⁶ The authors conclude, “Our findings suggest that from the standpoint of risk of dependency, clinicians prescribing tramadol for acute pain should exercise a level of caution similar to that surrounding the prescribing of other short acting opioids, including those on higher Drug Enforcement Administration schedules.”³⁶⁷

- A. Persistent medical use of opioids is a risk factor for addictive use. Short-term tramadol prescribing leads to persistent use, especially as doses increase. Thiels reported that receipt of tramadol alone was associated with a 6% increase in the risk of additional opioid use relative to other short-acting opioids; a 47% increase in the risk of persistent opioid use (defined as episodes of use lasting 90 or more days, that started in the 180 days following surgery); and a 41% increase in the most stringent category of persistent use (the CONSORT criteria; opioid use lasting at least 90 calendar days and including either 10 or more opioid fills or 120 or more days supply); all of these increases met criteria for statistical significance.³⁶⁸ Thiels also reported that doses of 300 MME and larger were associated with higher risk of prolonged use(odds ratios 1.1 to 1.6, see appendix F).³⁶⁹ This aligns with CDC data supporting the conclusion that the risk of prolonged use increases significantly when patients receive prescriptions for more opioids.³⁷⁰
- B. Tramadol manufacturers coached sales representatives to push higher doses: “Key Points: 100 mg is only starting

³⁶⁶ Thiels CA, et al. Chronic use of tramadol after acute pain episode: cohort study. *BMJ* 2019;365: i1849, 1-10 at pp. 5-6.

³⁶⁷ *Id.* at p. 6.

³⁶⁸ *Id.*, at p. 1.

³⁶⁹ *Id.*,at p. 6.

³⁷⁰ Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* 2017;66:265–269

dose for most patients – will likely need to go to 200 or 300 mg. Sample Detail: ‘So if we go back to that 50 year old female patient with chronic OA pain, for whom scheduled narcotics are inappropriate does it make sense to prescribe ULTRAM ER and use it on a daily basis to provide effective pain relief? Good. There are three strengths – 100, 200 and 300mg. For patients not already on tramadol, you want to start on 100mg, increasing the dose by 100mg increments every 5 days. The 100 mg dose is just a starting dose for most patients.’³⁷¹

- xii. Lay press articles have detailed widespread tramadol misuse, addiction, and diversion abroad. For example, a 2015 article reported that tramadol was “ubiquitous” in Egypt, and a clinic physician stated that up to 40% of his patients were “addicted” to tramadol.³⁷² Another tramadol article reported that “Fueled by cut-rate Indian exports and inaction by world narcotics regulators, tramadol dependency extends across Africa, the Middle East and into parts of Asia and eastern Europe.”³⁷³ The same article reported that, in the US, emergency room visits related to tramadol had tripled between 2005-2011, and that, in Northern Ireland, “tramadol is killing more people than heroin.”³⁷⁴ These sources provide additional support for the conclusion that tramadol is an addictive and dangerous drug.
 - xiii. The misleading message that tramadol is a “non-narcotic” penetrated the medical literature, including government reports and peer reviewed clinical studies, creating a false sense of safety about tramadol.
- A. In a September 2011 Government Accountability Office Report to Congressional Requesters on the problem of

³⁷¹ JAN-TX-00001492, produced natively at *12.

³⁷² Drug Abuse in Egypt: A pill for work and play, The Economist, April 18, 2015.

³⁷³ Justin Scheck, Tramadol: The opioid crisis for the rest of the world, Wall St. J., Oct. 19, 2016.

³⁷⁴ *Id.*

‘doctor shopping’, tramadol is listed in Table 1 as a “non narcotic painkiller.”³⁷⁵

- B. Yet within the report tramadol is among the most common drugs that patients engaged in ‘doctor shopping’ to obtain, fifth behind hydrocodone, oxycodone, morphine, and fentanyl, in a list of fourteen highly addictive prescription drugs.³⁷⁶
 - C. J&J’s own published studies included misleading claims based on tramadol’s non-scheduled status. For example, a 2007 study by Ortho-McNeil Janssen employees stated, “Concerns about regulatory scrutiny can cause the underprescription of conventional opioids and subsequent unrelieved or undermanaged pain. Thus, tramadol may be an option to postpone the use of conventional opioids while providing effective pain relief.”³⁷⁷ This statement is misleading in that it differentiates between tramadol and “conventional opioids,” when in fact tramadol’s mechanism of action includes the M1 metabolite that acts in the same manner as a “conventional opioid,” and it promotes such use on the basis that “regulatory concerns” would thereby be avoided—a coded reference to the tramadol’s non-scheduled status, which J&J had been instructed not to use in its promotion of the drug.³⁷⁸
- xiii. I personally experienced the marketing message that tramadol was not an opioid and was therefore safer and less addictive than opioid pain medications. It is my opinion that my experience was not unique, and that similar or identical messages were conveyed to the medical community in general. Tramadol prescribing went up between 2009 and 2017, even as prescribing of other opioids went

³⁷⁵ US. Government Accountability Office. (2011, September). Medicare Part D: Instances of questionable access to prescription drugs, (Publication No. GAO-11-699) at p. 11, <https://www.gao.gov/new.items/d11699.pdf>,

³⁷⁶ *Id.*, at Table 2, p. 12.

³⁷⁷ Vorsanger G, et al., Post hoc analysis of a randomized, double-blind placebo-controlled efficacy and tolerability study of tramadol extended release for the treatment of osteoarthritis pain in geriatric patients. *Clin Ther* 2007; 29:2520-2535, at p. 2530.

³⁷⁸ FDA-CDER. NDA 20-281 File. (March 3, 1995), https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020281Orig1s000rev.pdf.

down.³⁷⁹ With growing national awareness of the opioid epidemic, J&J promoted tramadol as a ‘safer alternative’, despite evidence of abuse, addiction, and risk of other serious side effects.

- A. As tramadol prescribing went up, so did reports of harm, including addiction and death, as described below.
- B. An independent Steering Committee tasked with monitoring tramadol after it went on the market found multiple reports of severe opioid withdrawal following tramadol (Ultram) cessation. Further, in some cases patients were exhibiting symptoms of withdrawal “not normally observed in opiate withdrawal, such as hallucinations, paranoia, extreme anxiety, panic attacks, confusion and unusual sensory experiences such as numbness and tingling in one or more extremities. Withdrawal symptoms of either type were one of the more prevalent adverse events associated with chronic Ultram use, comprising nearly 40% of all adverse events reported with Ultram. Most of these consisted of typical opiate withdrawal symptoms, but 1 in 8 cases presented as atypical. These results indicate that physicians and other healthcare professionals need to be aware of the potential of Ultram to induce withdrawal of the classical opioid type, and that atypical withdrawal may also occur.”³⁸⁰
- C. A study from the United Kingdom showed prevalence of tramadol users increased from 2000 to 2015, and then significantly reduced after tramadol was made a Schedule IV drug (2014). “Both annual tramadol utilisation and rate of tramadol-related deaths increased before tramadol classification and decreased thereafter.”³⁸¹

³⁷⁹ Thiels, “Chronic Use of Tramadol”, fn. 366, above, at Figure 1.

³⁸⁰ Senay EC, *et al.* Physician dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. *Drug and Alcohol Dependence* 2003;69:233-241, at p. 233.

³⁸¹ Chen T-C, *et al.* A 15-year overview of increasing tramadol utilization and associated mortality and the impact of tramadol classification in the United Kingdom. *Pharmacoepidemiol Drug Saf.* 2018;27:487-494, at p. 487.

- D. A 2010 study analyzed tramadol poisoning data from 2003-2009 in the States of West Virginia, Ohio, Kentucky and Arkansas. In 2007-08, Kentucky and Arkansas imposed Schedule IV status on tramadol (several years before the FDA acted to do so), while tramadol remained unscheduled in West Virginia and Ohio.³⁸² The study showed that poisonings due to tramadol rose in West Virginia and Ohio throughout the study period, while tramadol poisonings rose in Kentucky and Arkansas only until Schedule IV status was imposed, and declined thereafter.³⁸³ This study period was contemporaneous with the publication of the Vorsanger article promoting the use of tramadol as an alternative to “scheduled” opioids.
- j. In addition to being falsely marketed as non-narcotic and safer/less addictive than other opioids, tramadol was also falsely marketed as safer than non-opioid pain medications like acetaminophen and ibuprofen.
 - i. From Ultram ER Core Visual Aid Tour: “Sample Detail: ‘ULTRAM ER gives you added confidence due to its safety profile. As you know from your experience with tramadol, ULTRAM ER is not a scheduled product and is not associated with the GI or CV warnings of NSAIDs or COX-2s, and ULTRAM ER can be used safely for long term therapy. Please make sure you are familiar with this important Safety Information before you prescribe ULTRAM ER.’³⁸⁴
 - ii. Because of tramadol’s unique metabolism and mechanism of action, it poses additional risks that do not occur with standard non-opioid medications like acetaminophen and ibuprofen.
- A. The enormous inter-individual variability in CYP2D6 metabolism means that tramadol imposes risks on some patients that are greater than the risks for others, because the degree of metabolism in a given individual is

³⁸² Spiller HA, et al. Effect of scheduling tramadol as a controlled substance on poison center exposures to tramadol. *Annals of Pharmacotherapy* 2010;44:1016-1021, at p 1017

³⁸³ *Id.*, at pp.,1018, 1020.

³⁸⁴ JAN-TX-00001492, produced natively at *10

unpredictable and unknown prior to the patient's experience of an adverse event. Poor metabolizers won't get sufficient analgesic effects of tramadol, and thus can be left without pain relief. Rapid metabolizers will effectively get more opioids, making them more vulnerable to toxicity.³⁸⁵

- B. Case reports of pediatric patients with overactive CYP2D6 enzymes dying from tramadol have been reported. "These ultra-rapid metabolizers experience an increase in the production of active metabolites of codeine and tramadol, which can lead to oversedation, respiratory depression, and death."³⁸⁶ As a result, in 2017, the U.S. Food and Drug Administration updated their warnings regarding tramadol use, making tramadol contraindicated in patients under 12 years of age.³⁸⁷
 - C. Further, administering tramadol with other medications increases the unpredictability of its metabolism. "Comedication may compromise drug safety by increasing the risk of drug interactions and adverse events, a fact often underestimated in patients. Comedication can produce enzyme induction or inhibition mimicking genetic defects, which also contributes to the variable response to drugs."³⁸⁸
- iii. Tramadol carries the additional risk of seizures³⁸⁹ and life-threatening hypoglycemia.³⁹⁰ These are not risks typically seen with other analgesics, opioids and non-opioids alike.

³⁸⁵ Stamer UM, et al. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. *Clinical Pharmacology & Therapeutics* 2007;82(1):41-47.

³⁸⁶ Fortenberry M, et al. The use of codeine and tramadol in the pediatric populations – what is the verdict now? *J Pediatr Health Care* 2019;33:117-123, at p. 117

³⁸⁷ *Id.*

³⁸⁸ Stamer, "Concentrations of tramadol", fn. 385, above, at p. 45.

³⁸⁹ Ryan NE, Isbister GK. Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. *Clinical Toxicology* 2015;53:545-550, at p. 545.

³⁹⁰ Fournier J-P, et. al. Tramadol use and the risk of hospitalization for hypoglycemia in patients with noncancer pain. *JAMA Intern Med.* 2015;175(2):186-193, at p. 186.

- iv. Zeng *et al.* found: “Among patients aged 50 years and older with osteoarthritis, initial prescription of tramadol was associated with a significantly higher rate of mortality over 1 year of follow-up compared with commonly prescribed nonsteroidal anti-inflammatory drugs, but not compared with codeine.”³⁹¹
- k. The Pharmaceutical Opioid Industry has relied on flawed and industry-influenced studies regarding the risk of addiction from prescription opioids. The studies relied on by Defendants to estimate the risk of addiction from prescription opioids provide a significant underestimation of the true risk of misuse, dependence, and addiction for several reasons:
 - i. Many studies, particularly trials conducted by opioid manufacturers, screen out patients at higher risk of addiction, who are not commonly screened from real world clinical exposure.
 - ii. Many studies are not designed *a priori* to identify addiction outcomes, which means that they lack methodology to diagnose or otherwise accurately account for the cases.
 - iii. Many studies are sponsored and/or written by industry authors, raising conflict of interest and bias issues.
 - iv. Many studies are too short to assess addiction risk (as discussed previously).
 - v. Many studies do not use rigorous detection methods.
 - A. Most studies rely solely on patient questionnaire responses to identify problematic behavior, despite generally accepted knowledge that a significant subset of respondents will not disclose behaviors of interest that could subject them to stigma, sanction, or both, as exemplified by the Fleming study (discussed above, and below).
 - B. A retrospective study of urine toxicology information for 122 patients maintained on chronic opioid therapy, found

³⁹¹ Zeng C, *et al.* Association of tramadol with all-cause mortality among patients with osteoarthritis. *JAMA* 2019;321(10):969-982, at p. 969.

that 43% of patients had a “problem” with opioids: positive urine toxicology or one or more aberrant drug taking behaviors. The authors concluded “Monitoring both urine toxicology and behavioral issues captured more patients with inappropriate drug-taking behavior than either alone. Requiring a report of behavioral issues and urine toxicology screens for patients receiving chronic opioids creates a more comprehensive monitoring system than either alone.”³⁹²

- C. Urine drug tests provide more reliable evidence of drug misuse and addiction than patient report. Fleming found a 24% rate of positive toxicology tests for illicit drugs. “Eighty-four of 185 (46%) patients with positive toxicology testing denied illicit drug use during the research interview, even when they were guaranteed anonymity. This finding confirms clinical observations that patients with chronic pain often mislead their physicians about illicit drug use Minimization of drug use and drug problems by patients is a major concern in all studies that try to estimate rates of addiction, especially for illegal drugs.”³⁹³ In other words, rates of opioid use disorder were potentially 8 times higher in the same population when objective measures of urine drug screens were used.
- D. Databases with information on prescribing of controlled substances provide more reliable evidence of drug misuse and addiction than patient report. Checking a database with access to this information gives more reliable evidence on duplicate prescriptions, early refills, “doctor shopping,” and other indicators of misuse and addiction.³⁹⁴

³⁹² Katz NP, Sherburne S, Beach M, *et al.* Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. *Anesth. Analg.* 2003. doi:10.1213/01.ANE.0000080159.83342.B5, at p. 1097.

³⁹³ Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance Use Disorders in a Primary Care Sample Receiving Daily Opioid Therapy. *J Pain.* 2007. doi:10.1016/j.jpaa.2012.02.008, at pp. 580-581.

³⁹⁴ Ctrs. for Disease Control and Prevention, What States Need to Know about PDMPs. <https://www.cdc.gov/drugoverdose/pdmp/states.html>.

1. A particularly flawed article is the 2008 review by Fishbain, which claimed that the risk of addiction from chronic use of prescription opioids is 3.27% overall; 0.19% if considering de novo opioid users only.³⁹⁵ Overall, Fishbain included 67 studies in his review and analysis of various measures of addiction or abuse. With respect to the 3.27% / 0.19% addiction rates, Fishbain stated that he relied on a subset of 24 studies with a total of 82 addiction cases among 2,507 patients, identified in Appendix 1 to the article, accessed at the journal website. However, review of the Appendix 1 table shows only 23 studies with 81 addiction cases among 2173 patients, resulting in a prevalence of 3.73%, rather than 3.27%. These figures are not reliable indicators of true prevalence of OUD, for the reasons explained below.
 - i. The Fishbain analysis included studies that (a) were too short to accurately assess addiction risk; (b) administered low doses; (c) screened out patients at higher risk of addiction; (d) were not designed to identify addiction; (e) did not apply rigorous detection methods; and (f) were sponsored and/or written by industry authors, raising conflict of interest and bias issues.
 - ii. Fishbain's pooled analysis found substantially higher evidence of drug misuse/addiction (14.5%) when findings were based on the more objective measure of aberrant urine toxicology screens.³⁹⁶
 - iii. Fishbain's 2008 review omitted two studies from his 1992 review that had reported substantially higher prevalence than the pooled figure of 3.27% stated in the 2008 article. Studies by Evans, *Anesthesia* 1981; 36:597-602,³⁹⁷ (reported 16% addiction in Fishbain's 1992 article³⁹⁸), and Katon, *Am J Psychiatry* 1985;

³⁹⁵ Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? a structured evidence-based review. *Pain Med.* 2008; 9(4):444-459. doi:10.1111/j.1526-4637.2007.00370.x, at p. 444.

³⁹⁶ *Id.* at p. 450.

³⁹⁷ Evans PJD. Narcotic addiction in patients with chronic pain. *Anaesthesia*. 1981;36(6):597-602. doi:10.1111/j.1365-2044.1981.tb10323.x.

³⁹⁸ The Evans article states that the addiction rate was 7%, which appears to be based on 9 cases among the full study population of 130 subjects. (Evans at p. 600) Fishbain's 1992 article states, "Of 56 chronic *benign* patients, 9 or 16% exhibited features of addiction." (Fishbain 1992, Table 4, at p. 83; emphasis added). Thus, comparing the

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142:1156-60, (reporting 18.9% addiction)³⁹⁹, both appeared in Fishbain 1992 but were omitted from Fishbain 2008. Further, the Evans study, in turn, cited to an article by Maruta, *Mayo Clinic Proceedings* 1976; 54:241-4,⁴⁰⁰ which reported an incidence of 24% addiction among a chronic pain population.⁴⁰¹ Fishbain 2008 stated that his search for relevant articles went back to 1966, so these three references would have been within the time period he searched. Fishbain was a litigation consultant for Defendant Purdue between at least 2005-2008, a relationship that was not disclosed in the 2008 article, and which casts the exclusion of the higher prevalence studies in a disturbing light.

- iv. In 1992, Fishbain had published an earlier study of addiction risk with chronic opioid exposure, which stated, “According to the results of this review, to date, only three studies have attempted to address the concepts of psychological dependence and compulsive use, *i.e.*, addiction, in an acceptable fashion. These studies have found a prevalence from 3.2% to a high of 16% for the possibility of addiction in chronic pain patients.”⁴⁰² The same article also stated, ‘It is interesting to note that the only two studies to utilize urine toxicologies found illicit drug use in 6.41 and 12.5% of their chronic pain patients. These results may therefore indirectly support the results of the other ‘addiction’ studies described earlier, as they are both within the prevalence percentages derived from these studies.’⁴⁰³ However, these higher prevalence figures, and

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two articles, it appears that Evans included the 74 cancer patients, who had no reported cases of addictive behavior, in the total of 130 subjects. Conversely, Fishbain 1992 limited his study to “Drug Abuse, Dependence, and Addiction in *Chronic Pain Patients*,” (emphasis added); thus the figure of 16% (9/56) appears accurate.

³⁹⁹ Egan K, Katon W. Chronic Pain: Lifetime Psychiatric Diagnoses and Family History. *Am J Psychiatry*. 1985;(October):1156-1160, at p. 1157.

⁴⁰⁰ Note that the Maruta article was actually published in 1979, and the cite in the Evans article lists the incorrect year of publication.

⁴⁰¹ Maruta T., Swanson D., Finlayson, R. Drug Abuse and Dependence in Patients with Chronic Pain. *Mayo Clin. Proc.* 1979 (April):241-244, at p. 242.

⁴⁰² Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. *Clin J Pain*. 1992. doi:10.1097/00002508-199206000-00003, at p. 80.

⁴⁰³ *Id.* at p. 81.

the sources from which they came, were omitted from Fishbain's 2008 analysis.

- v. Also, Fishbain's 2008 review⁴⁰⁴ included data from a 1992 study by Bouckoms, *et al.*, which found that 14 of 59 clinic patients (24%) taking opioids for long-term met criteria for "narcotics addiction."⁴⁰⁵ Bouckoms also stated: "The influence of population sample bias in prevalence studies of narcotic addiction is dramatically shown in a comparison of studies in the literature. Table 5 summarizes data from the studies of Porter, Maruta, Taub, Evans, Langemark, and Portenoy, wherein the prevalence of addiction was 0.03%, 24%, 4.2%, 7%, 35%, and 5%, respectively."⁴⁰⁶ Notably, the 0.03% figure in Bouckoms' text is based on the Porter and Jick 1980 Letter⁴⁰⁷—the only one of the 5 references that was *not* based on a population of patients treated with opioids for chronic pain.
- vi. All of the sources cited by Bouckoms were available to Defendants from 1992 on. Yet their promotional statements beginning in the 1990s cited the inapt Porter and Jick study⁴⁰⁸ of hospitalized patients with any exposure to opioids, regardless of duration, as the source for the claim of "less than one percent" prevalence of addiction. I am not aware of any Defendants having issued a promotional statement citing the results of 24%, 4.2%, 7%, 35% or 5%, referenced by Bouckoms in 1992.⁴⁰⁹ Nor am I aware of any such statements by Defendants that cited the range of "prevalence from 3.2% to a high of 16% for the possibility of addiction" reported by Fishbain in 1992.⁴¹⁰ The timeline below shows the dates of publications demonstrating far greater risks of addiction to

⁴⁰⁴ Fishbain, *et al.*, "What Percentage," fn. 395, above.

⁴⁰⁵ Bouckoms AJ, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic nonmalignant pain treated with long-term oral narcotic analgesics. *Ann Clin Psychiatry*. 1992. doi:10.3109/10401239209149570, at p. 185.

⁴⁰⁶ *Id.* at p. 188.

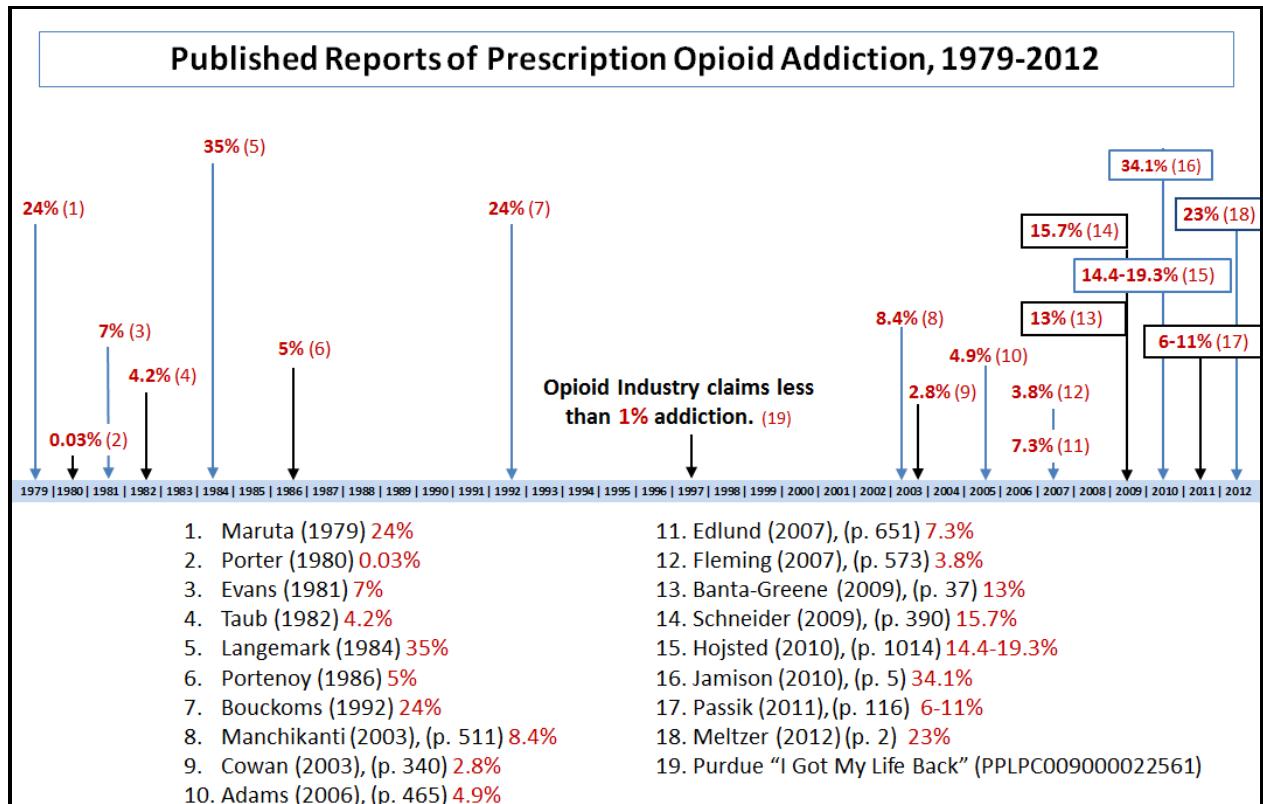
⁴⁰⁷ Porter, Jick, *et al.*, "Addiction Rare," fn. 75, above, at p. 123.

⁴⁰⁸ *Id.*

⁴⁰⁹ Bouckoms, *et al.*, "Chronic Nonmalignant," fn. 405 above, at p. 188.

⁴¹⁰ Fishbain, *et al.*, "Drug Abuse," fn. 402, above, at p. 80.

prescription opioids than those misrepresented by Defendants. Further, the timeline below illustrates that risks were known and published in the peer-reviewed literature well before the 1990s, when the Pharmaceutical Opioid Industry began their misleading marketing of addiction rates that were “less than 1%,” “rare,” “nonexistent,” or “negligible” (see references at 7.b above):



- vii. Fishbain made an admittedly “arbitrary” decision to apply a 65% “quality score” requirement, despite his own reference to a source stating that studies with scores below 50% are generally not used.⁴¹¹ The Tables in the Appendix to the Fishbain 2008 article provide the quality scores only for the studies that were included, but not for those that were excluded, so it cannot be determined whether the three higher prevalence studies were excluded for

⁴¹¹ Fishbain, *et al.*, “What Percentage,” fn.395, above, at p. 448.

failure to meet the arbitrary quality score threshold, or for other reasons. Their absence from the 2008 review casts further doubt on its reliability.

- m. Another flawed and biased study that was reviewed by Fishbain was co-authored by Portenoy.⁴¹² In this study, 27 physicians who attended training sessions to serve on “a pain-oriented speakers’ bureau” applied a “Pain Assessment and Documentation Tool” (PADT) to 388 of their patients, with diverse pain syndromes, who had been on various regimens of chronic opioid therapy for at least 3 months.⁴¹³ The physicians reported their assessment that 5.93% (23/388) of their patients were addicted.⁴¹⁴ However, the doctors also reported that 19.3 % (75/388) engaged in 3 or more “aberrant drug-taking behaviors,” such as requests for early renewals, increasing doses without authorization, reporting lost or stolen prescriptions, obtaining medications from other doctors, declining physical/social/psychological function, over-sedation, etc.; and that 10.8% (41/388) engaged in 5 or more such behaviors.⁴¹⁵ Their conclusion of 5.93% addicted lacks validity for several reasons.
 - i. Appendix 1 states: “Of the total sample 5.93% were thought to demonstrate opioid prescription abuse/ addition [sic].”⁴¹⁶ This is not correct, since the 5.93% applies solely to addiction, whereas the abuse rates were much higher, as described above.
 - ii. Other studies on Fishbain’s reference lists would count such behaviors as evidence of addiction, such that the addiction rate in the Passik study would be about 2 to 4 times greater than the 5.93% rate based on the doctors’ reports. Including the full range of opioid use disorder (mild, moderate, severe) based on DSM-5 criteria, this study’s summative results (5.93% + 19.3% +10.8%) demonstrate that 36.06% of patients met DSM-5 criteria for opioid

⁴¹² Passik SD, Kirsh KL, Whitcomb L, *et al.* Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the Pain Assessment and Documentation Tool. *J Opioid Manag.* 2005.

⁴¹³ *Id.* at p. 258.

⁴¹⁴ *Id.* at p. 263.

⁴¹⁵ *Id.* at pp. 260-261.

⁴¹⁶ *Id.* at Appendix I, p. 47.

- use disorder, approximating the 40% rate of opioid use disorder consistent with the Boscarino, *et al.* study⁴¹⁷ described above.
- iii. The possibility of underestimating the addiction rate is of particular concern in light of the participating physicians' roles as Speakers' Bureau trainees.
 - n. In yet another flawed study reviewed by Fishbain *et al.*, 10 patients, who had been treated for chronic noncancer pain (CNCP) with morphine for an average of 2 years, participated in a study alternating between one 60 hour period of morphine and one 60 hour period of placebo (two and a half days each).⁴¹⁸ "When asked 'Do you have any drug craving?' (graded as mild, moderate or severe), no patients reported craving for morphine or a compulsion to take any," during the period of cessation of opioids.⁴¹⁹ The authors concluded from these data "that there exists a group of CNCP patients whose long-term opioid consumption can be beneficial and remain moderate without them suffering from the consequences of problematic opioid drug use."⁴²⁰ Appendix 1 states: "0% demonstrated psychological dependence."⁴²¹ This conclusion lacks validity for several reasons.
 - i. The short duration without opioids is insufficient to assess "problematic opioid drug use." This methodology might detect physical dependence and withdrawal, but not addiction. Addiction is a chronic relapsing and remitting illness evidenced by a pattern of behavior over weeks to months, not hours to days.
 - ii. Craving and withdrawal are very subjective and not diagnostic of addiction. Further, asking study subjects about "craving" is likely to bias their response: "craving" is a loaded term associated with

⁴¹⁷ Boscarino, *et al.*, "Opioid-use disorder," fn. 314, above, at p. 83.

⁴¹⁸ Cowan DT, Wilson-Barnett DJ, Griffiths P, Vaughan DJA, Gondhia A, Allan LG. A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. *Pain Med.* 2005. doi:10.1111/j.1526-4637.2005.05020.x, at p. 113.

⁴¹⁹ *Id.* at p. 116.

⁴²⁰ *Id.* at p. 119.

⁴²¹ *Id.* at Appendix 1.

- addiction. Patients would be savvy enough to want to avoid this pejorative label.
- iii. This British study was funded by Janssen-Cilag, introducing inherent bias.⁴²²
 - iv. Although this is a small study that would have little overall impact on the pooled analysis, it is worth attention if only to demonstrate the contradiction between Fishbain's inclusion of an almost absurdly brief study of 60 hours of exposure, while omitting relevant studies with higher prevalence that he personally cited in his earlier review article.
 - o. Higgins, *et al.*, performed a meta-analysis of incidence of addiction studies, that is, addiction diagnosed in a pre-specified period of time following the initial exposure to a prescription opioid. The authors argued for a 4.7% overall incidence of iatrogenic addiction to prescription opioids,⁴²³ but their findings need to be considered in light of a number of limitations.
 - i. Higgins did not account for the role of dose and duration as the main cause of opioid use disorder. In particular, Higgins claimed to rely on the Edlund (2014) study for an incidence rate of 0.2%, while omitting Edlund's finding that the rate in his healthcare database study was 50 times higher for those who were exposed to chronic (>90 days) high dose (>120 MME), compared to patients with only acute exposures (over 6% for the former, compared to 0.12% for the latter). Edlund noted that it was "almost meaningless to talk of a single 'rate'"⁴²⁴ under these circumstances, yet that is precisely what Higgins did. Similarly, Higgins cited the Cepeda (2013) study for an overall rate of 0.5%, ignoring that this healthcare database study included all patients who "initiated" opioid therapy, without analysis of variations in rates between patients with different doses and durations of exposure.

⁴²² *Id.* at p. 113.

⁴²³ Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. *Br J Anaesth.* 2018;120(6):1335-1344. doi:10.1016/j.bja.2018.03.009, p. 1339.

⁴²⁴ Edlund, "Role of Opioid Prescription", fn. 59, above, at p. 562.

- ii. Incidence will inevitably under-report the number of cases in a population, because it will only examine data for a fixed beginning and endpoint; whereas prevalence is the more accurate marker of the number of cases existing in a population at a given point in time, including all cases of addiction among the population taking prescription opioids.
- iii. New onset opioid use disorder (incidence) does not take into account the harm done to patients who maintain or relapse to opioid addiction as a result of medical exposure to opioids. That is, continued exposure imposes continued risk of misuse, dependence, overdose, and the panoply of ill effects of chronic opioid therapy described herein.
- iv. The authors speculate that the pooled rate was higher for the studies of “weak” opioids than for “strong” opioids because the subjects might have displayed “pseudoaddiction,”⁴²⁵ i.e., because the opioids were weak, they displayed drug-seeking behaviors to alleviate their pain that were misconstrued by the physicians, rather than because of a use disorder. The report of a higher rate with lower doses is an unreliable, outlier finding that contradicts numerous large, well-done studies demonstrating the dose-response relationship between higher opioid dose and greater addiction and mortality. Also, Higgins’ comparison of “weak” versus “strong” opioids failed to meet standard methods of comparing the dose of prescription opioids according to their milligrams morphine equivalent, or MME.
- v. The authors’ restrictive criteria resulted in only 12 studies having been included⁴²⁶ compared to others (e.g., Vowles), who included 38 studies.
- vi. The authors erroneously stated that Vowles reached a similar conclusion as to the rates of addiction (4.3 v. 4.7%),⁴²⁷ when in

⁴²⁵ *Id.* at p. 1343.

⁴²⁶ *Id.* at p. 1335.

⁴²⁷ *Id.* at p. 1342.

fact Vowles reported rates of addiction as 8-12%,⁴²⁸ or approximately 21-29% when the spectrum of mild through severe OUD is included.

- vii. Two of three authors report pharma consulting, including Pfizer.⁴²⁹
- p. The 2010 Cochrane Review by Noble *et al.* (2010), stated that opioid addiction occurred in “0.27% of participants in the studies that reported that outcome,”⁴³⁰ and “... serious adverse events, including iatrogenic opioid addiction, were rare.”⁴³¹ However, the underlying studies in the Cochrane Review that were selected for analysis were predominantly funded by the manufacturers and were neither intended nor designed to detect addiction risks. As detailed below, estimates based on those studies are unreliable and unrealistically low.
 - i. The Cochrane 2010 review analyzed 26 studies with 27 treatment groups that enrolled a total of 4,893 participants. Twenty five of the studies were case series or uncontrolled long-term trial continuations. The other was an RCT comparing two opioids.⁴³² Only 8 of the 26 included studies provided data on addiction: Allan; Anderson; Hassenbusch; McIlwain; Milligan; Mystakidou; Portenoy; and Zenz.
 - ii. Only one of these studies (Portenoy, 2007)⁴³³ was *a priori* designed to assess risk of opioid use disorder/addiction. The rest were designed to assess pain efficacy, and addiction risk was an afterthought. Further, none applied rigorous detection methods, or in most cases any detection methods at all to assess opioid misuse or addiction. All of the studies excluded patients with a history of alcohol or substance use disorders. Seven of the eight studies were

⁴²⁸ Vowles, *et al.*, “Rates of Opioid Misuse,” fn. 290, above, at p. 569; McNicol, *et al.*, Cochrane Review 2013, fn. 220, above, at p. 28.

⁴²⁹ Higgins, *et al.*, “Incidence of Iatrogenic,” fn. 423, above, at p. 1343.

⁴³⁰ Noble, *et al.*, “Long Term Opioid Management,” fn. 205, above, at p. 9.

⁴³¹ *Id.* at p. 2.

⁴³² *Id.* at p. 1.

⁴³³ Portenoy, *et al.*, Long Term Use of Controlled-release Oxycodone for Noncancer Pain: Results of a 3-year Registry Study. *Clin. J. Pain* 2007; 23: 287-299, DOI: 10.1097/01.brs.0000186860.23078.a8.

sponsored and/or written by industry authors, raising conflict of interest and bias issues.

- iii. Below, I address in detail each of the eight studies providing data on addiction that were included in the 2010 Cochrane Review.

A. Allan *et al.* compared efficacy and safety of transdermal fentanyl and sustained release morphine in opioid naïve patients with chronic low back pain over 13 months.⁴³⁴ Classification as “opioid naïve” was based on the patient receiving limited opioids in the 4 weeks prior to the study, with no screening for opioid use prior to 4 weeks.⁴³⁵ Opioid misuse and addiction did not warrant listing in the Adverse Event “Table 8.”⁴³⁶ In other words, it was not a variable the authors were measuring, as corroborated by the absence of any instrument to assess addiction, despite the use of other survey questionnaires used to track other adverse events.

- I. Yet the authors claimed “Addiction was not reported as an adverse event for any participant.”⁴³⁷ The authors further stated “No cases of addiction were reported as an adverse event; this is in line with other studies, which have shown that opioids can be used in chronic noncancer pain without significant risk of abuse. [citing Jamison *et al.*, *Spine* 1998].”⁴³⁸
- II. The authors’ conclusions are not reliable based on methodologic inadequacies to assess for addiction risk. Even when investigators are attempting to detect addiction and abuse, as in the studies described above, the difficulties are daunting, as

⁴³⁴ Allan L, Richarz U, Simpson K, Slappendel R. Transdermal Fentanyl Versus Sustained Release Oral Morphine in Strong-Opioid Naïve Patients With Chronic Low Back Pain. *Spine* 2005; 30(22):2484-2490, at p. 2484.

⁴³⁵ *Id.* at p. 2485.

⁴³⁶ *Id.* at p. 2488.

⁴³⁷ *Id.*

⁴³⁸ *Id.* at p 2489.

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indicated by reports of patient concealment of problem behaviors and substantial disparities between questionnaire responses and urine drug screening; when researchers do not look for addiction and abuse, they are quite unlikely to find such evidence. Further, the study was underwritten by Janssen pharmaceuticals, the makers of Duragesic, transdermal fentanyl, suggesting bias conferred by industry sponsorship.⁴³⁹

- B. Anderson *et al.* followed 30 patients prospectively for 24 months to assess the long-term safety and efficacy of chronic intrathecal morphine (injected into the spinal canal, or into the subarachnoid space so that it reaches the cerebrospinal fluid) in the treatment of chronic pain.⁴⁴⁰ Patients with “psychopathological or substance abuse problems” were screened out and deemed ineligible. Questionnaires were used to track many different variables, but none asked about signs and symptoms of opioid use disorder.
 - I. The authors report that one patient (1/30, 3%) “was withdrawn from therapy because of drug-seeking behavior . . .”⁴⁴¹ This patient “complained of continually escalating pain after infusion system implant, despite successful pain relief during trial at an epidural dose of less than 10mg per day . . . and sought to obtain oral narcotics from other health care providers,” although the authors do not disclose how they obtained this information. When further requests for dose increases were denied, the patient dropped out of the study.⁴⁴²

⁴³⁹ *Id.* at p. 2484.

⁴⁴⁰ Anderson VC, Ph D, Burchiel KJ. Prospective Study of Long-term Intrathecal Morphine in the Management of Chronic Nonmalignant Pain. *Neurosurgery* 1999;44(2), at p. 289.

⁴⁴¹ *Id.* at p. 292.

⁴⁴² *Id.* at pp. 295-296.

- II. The authors conclude “In general, the incidence of addiction among patients with nonmalignant pain receiving chronic opioid is low,” but their findings are unreliable given methodological failures to assess addiction risk. The study was sponsored by Medtronic, Inc., the makers of the intrathecal pump.⁴⁴³
- C. Hassenbusch, like Anderson, examined a case series of patients (22) with intrathecal opioid infusion pumps. In this case, they followed patients for 5 years.⁴⁴⁴ The same limitations described in the Anderson study apply here: patients with history of mental illness or addiction were excluded,⁴⁴⁵ and there were no screening instruments or any other detection method to assess for opioid misuse or addiction. Yet the authors conclude “There was no occurrence of opioid dependence, either physical or psychological . . .”⁴⁴⁶
- D. McIlwain *et al.* did a 52-week open label extension study of oxymorphone extended release (ER) in patients with moderate to severe chronic osteoarthritis related pain.⁴⁴⁷ The study was sponsored by Endo Pharmaceuticals, the makers of the study drug.⁴⁴⁸ The study did not use screening instruments or other detection methods for opioid misuse or addiction. Their Table 2 of adverse events did not include opioid misuse/addiction, despite including 11 other opioid-related adverse events.⁴⁴⁹ Despite the absence

⁴⁴³ *Id.* at p. 299.

⁴⁴⁴ Hassenbusch S, Stanton-Hicks M, *et al.* Long Term Intraspinal Infusions Of Opioids in the Treatment of Neuropathic Pain. *Journal of Pain and Symptom Management*. 1995;10:527-543, at p. 529.

⁴⁴⁵ *Id.* at p. 528.

⁴⁴⁶ *Id.* at p. 536.

⁴⁴⁷ McIlwain H, Ahdieh H. Safety, Tolerability, and Effectiveness of Oxymorphone Extended Release for Moderate to Severe Osteoarthritis Pain A One-Year Study. *Am J Ther*. 2005;112:106-112, p. 106.

⁴⁴⁸ *Id.* at p. 111.

⁴⁴⁹ *Id.* at p. 108.

of any method for detecting or measuring addiction risk, the authors concluded, “No instances of drug addiction or abuse were recorded.”⁴⁵⁰

- E. Milligan *et al.* studied 532 chronic noncancer pain patients (only 301 completed the trial) being treated with transdermal fentanyl for up to 12 months. They report “drug abuse/dependence” in less than 1% of their sample, but qualify this by saying, “none was considered definitely related to the treatment.”⁴⁵¹ Like the other studies included in the addiction risk assessment of the 2010 Cochrane review, this study was not designed to reliably assess addiction risk: patients with a history of substance abuse or psychiatric disorders were excluded, no screening or detection instruments for opioid misuse or addiction were described.⁴⁵²
 - I. The authors report three cases of “drug abuse (2 moderate and 1 severe)”; two cases of “moderate physical drug dependence (as opposed to abuse)”; and “no reports of addiction.”⁴⁵³ Yet how these concepts were defined and the cases detected are not clarified.
 - II. The study was supported by a grant from Janssen.⁴⁵⁴ Despite these serious flaws, the authors concluded, “There were no reports of addictive behavior in any of the patients during this long-term study. Because the fear of addiction is one of the reasons for the underuse of opioids in chronic noncancer pain, this study provides further evidence

⁴⁵⁰ *Id.* at p 109.

⁴⁵¹ Milligan K, Lanteri-minet M, Borchert K, *et al.* Evaluation of Long-term Efficacy and Safety of Transdermal Fentanyl in the Treatment of Chronic Noncancer Pain. *J Pain.* 2001;2(4):197-204 at p. 197, doi:10.1054/jpai.2001.25352.

⁴⁵² *Id.* at p. 198.

⁴⁵³ *Id.* at pp. 201-202.

⁴⁵⁴ *Id.* at p. 197.

that these fears are unfounded.”⁴⁵⁵ This conclusion does not follow from the evidence.

- F. The study by Mystakidou recruited 529 patients into an open-label study of transdermal therapeutic system-fentanyl (TTS-F) for 28 days, followed by an open-label follow-up for a median of 10 months between 1996-2002.⁴⁵⁶ The first page of the article includes the copyright symbol for the American Pain Society, which had been funded substantially by opioid manufacturers; the authors do not disclose a corporate sponsor, but they cite to prior studies of Dellemijn and Allan that acknowledged participation by Janssen-Cilag, the manufacturer of Duragesic TTS-F, and the Janssen Research Foundation.⁴⁵⁷
- I. A complete description of exclusion criteria was not provided; the authors stated only, “Exclusion criteria included a history of opioid abuse, surgery in the preceding 7 days or scheduled surgery, contraindications to opioids, and opioids use outside of the designated treatment regimen.”⁴⁵⁸ No information is provided as to what constituted “contraindications to opioids;” and the exclusion for “opioids use outside the designated treatment regimen” inherently eliminates the population with the most obvious defining characteristic of addiction.
- II. The authors state, “Following discontinuation from the study, no patient complained of withdrawal symptoms or was found to display dependency”,⁴⁵⁹; however, like the others described above, the

⁴⁵⁵ *Id.* at p. 203.

⁴⁵⁶ Mystakidou K, *et al.* Long-Term Management of Noncancer Pain With Transdermal Therapeutic System-Fentanyl. *J Pain*. 2003;4(6):298-306. doi:10.1016/S1526-5900(03)00632-1, at pp. 298-299.

⁴⁵⁷ *Id.* at p. 305.

⁴⁵⁸ *Id.* at p. 299.

⁴⁵⁹ *Id.* at pp. 300-301.

Mystakidou study included no protocol to detect addiction, withdrawal, dependency or abuse, either during the study or after discontinuation. Without such information, it is unknown whether patients experienced such effects during the study, nor whether they returned to their former opioid regimens after the study ended.

- G. Portenoy describes an open label continuation study using controlled release (CR) oxycodone (OxyContin) in a population of chronic pain patients who had previously participated in controlled trials of CR oxycodone for pain.
 - I. Unlike the other studies included in the 2010 Cochrane review, this study by Portenoy *et al.* included specific methods for assessing opioid misuse and addiction, including an independent review panel to determine types of problematic opioid use. However, the information evaluated by the independent review panel was based entirely on patient self-report, which we know to be inherently unreliable, particularly in the context of a clinical trial designed to assess pain efficacy.
 - II. The authors reported “6 of 227 (2.6%) patients could be considered to have probable drug abuse or dependence based on the independent expert review, none of whom met diagnostic criteria for substance abuse.”⁴⁶⁰ This appears to be the basis for the “3%” figure used in the Noble 2010 review. However, the article also reported that 133 patients dropped out of the study, so the use of 227 as the denominator is questionable. Further, “Patients with self-reported past or present substance or alcohol abuse” were excluded, as were patients with a “documented allergy to oxycodone or other

⁴⁶⁰ Portenoy, *et al.*, “Long Term Use,” fn. 433, above, at p. 296.

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opioids.”⁴⁶¹ Finally, the study was sponsored by Purdue Pharma, the makers of Oxycontin.⁴⁶²

- H. Zenz described 100 chronic nonmalignant pain patients who were given opioids in an open-label, non-controlled setting, between 1986-1990.⁴⁶³ Treatment was discontinued in 59 patients (21 did not respond to opioid therapy; 20 changed to an alternative treatment method; 10 were discontinued for “lack of compliance;” and 8 died during the study period).⁴⁶⁴
- I. Zenz reported, “There were no cases of respiratory distress or addiction to opioids.”⁴⁶⁵ As in the studies described above, Zenz had no protocol to look for or record addiction or abuse.
- II. No details were provided as to the type of “noncompliance” that caused 10 patients to be discontinued, but “noncompliance” in the setting of opioid therapy is a red flag for concern over signs of abuse as to which the lack of further information is another conspicuous weakness of the study.
- iv. In summary, the studies contributing to the addiction rate reported in the 2010 Cochrane review are subject to common inadequacies, primary among them their focus on efficacy, lack of any method to detect addiction or misuse, and the screening out of higher risk patients. Their data do not square with the much higher prevalence of OUD reported among real world chronic pain populations, by investigators who were looking for it.

⁴⁶¹ *Id.* at p. 288.

⁴⁶² *Id.* at p. 287.

⁴⁶³ Zenz M, et al. Long Term Oral Opioid Therapy in Patients with Chronic Nonmalignant Pain. *J Pain Symptom Manage.* 1992;7(2):69-77, at p. 70.

⁴⁶⁴ *Id.* at p. 73.

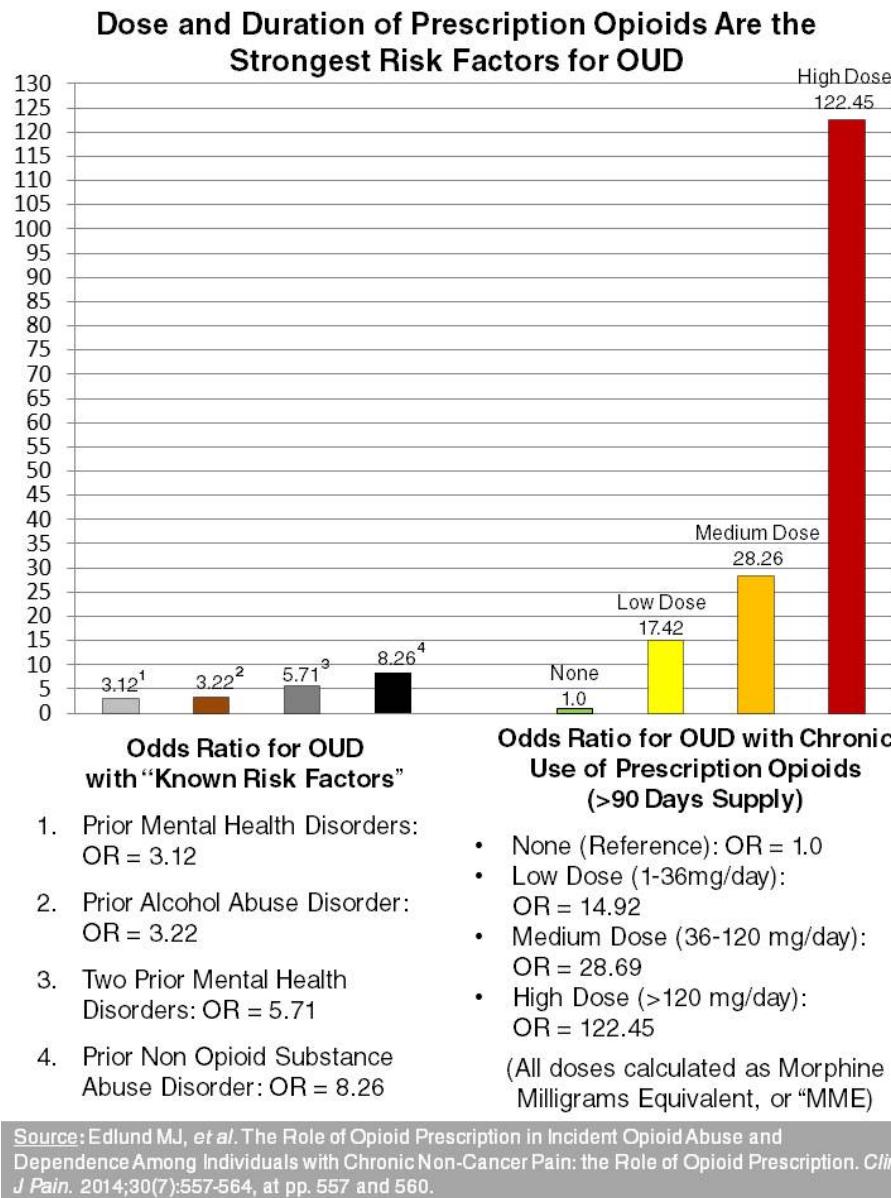
⁴⁶⁵ *Id.* at p. 69.

- v. As mentioned above, the 1980 New England Journal of Medicine letter to the editor entitled “Addiction Rare in Patients Treated with Narcotics,” reported only four cases of addiction among 11,882 patients treated with opioids.⁴⁶⁶ This letter did not represent relevant or reliable evidence of the risk of opioids for chronic non-cancer pain, because the article pertained to a hospitalized population, including patients who received no more than a single dose, rather than the outpatient chronic pain population for whom opioid use was promoted and became prevalent. Nonetheless, it influenced prescribers and was frequently quoted by the Pharmaceutical Opioid Industry in its advertisements for opioids in the treatment of chronic pain, as proving that “less-than-1%” of patients receiving opioids for pain becomes addicted. Defendants’ promotional messages continued to cite their “less-than-1%” claim, or that addiction with chronic opioid therapy was “rare,” despite numerous peer-reviewed studies to the contrary over a period of decades. (See Appendix I.)
- q. In summary, there is not, and has never been, scientific support for the claim that the risk of addiction from chronic opioid therapy is low, “rare,” or “less than 1%.” In fact, the best evidence available shows that the risk of addiction in patients taking opioids for chronic pain is between 10% and 30%. In teens and young adults, the evidence shows that even very limited exposure to prescription opioids can result in addiction
- r. The Pharmaceutical Opioid Industry also made inaccurate claims as to the validity of patient screening as a predictor of who will become addicted. The largest risk factors for addiction are dose and duration of opioid exposure, regardless of whether a particular patient may have identifiable risk factors in his or her social or genetic history. It is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. When it occurs in patients taking opioid medications for pain, addiction is neither easy to identify nor easily managed.
 - i. Over the years of increased use of opioids for chronic pain, as the epidemic of addiction has grown, a number of physicians have attempted to develop “screening” instruments that might identify

⁴⁶⁶ Porter, Jick, *et al.*, “Addiction Rare,” fn. 75, above, at p. 123.

patients at high risk of addiction, who could then be screened out of opioid therapy, or closely monitored if such therapy were instituted. However, even if screening for established risk factors were implemented, data support the conclusion that OUDs would not be eliminated. In the Edlund study, the odds ratio for the incidence of OUDs associated with chronic use, even at low doses, was far higher than the odds ratio for established risk factors that screening instruments attempt to identify. In particular, the odds ratios with chronic low dose use (14.92), medium (28.69), and high dose (122.45) were all substantially greater than the odds ratios for mental health diagnosis (3.12); multiple mental health diagnoses (5.71); prior alcohol use disorder (3.22); and prior non-opioid abuse disorder (8.26).⁴⁶⁷ For chronic/high dose opioid use, the odds ratio of approximately 122 is 40 times greater than for a mental health or alcohol use diagnosis, and 15 times higher than for a prior non-opioid use disorder. According to these data, the chronic use of opioids is responsible for far more OUDs than the existence of identifiable risk factors for OUDs. These data are shown in the graph below:

⁴⁶⁷ Edlund, *et al.*, “Role of Opioid Prescription,” fn.59, above, at p. 563.



- ii. It is true that *a priori* risk of addiction is related to genetics (a biological parent or grandparent with addiction), as well as complex psychosocial factors such as co-occurring mental illness, poverty, unemployment, multigenerational trauma, and peer influence. Persons with a history of addiction are more likely to develop problematic opioid use to the opioid their doctor is

prescribing.⁴⁶⁸ These risk factors notwithstanding, it is also true that addiction can occur in persons with none of these risk factors, and it is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. Hence, caution and monitoring are necessary for all patients being prescribed these medications, and even then will never be a failsafe method.

- iii. A validated screening instrument to predict which patients are more vulnerable to the adverse consequences of opioid therapy, including addiction, is theoretically of benefit, but to date, none has been shown to predict future adverse consequences. Kaye *et al.* summarizes the progress in a narrative review as follows: “Although several screening instruments and strategies have been introduced in recent years, there is no single test or instrument which can reliably and accurately predict those patients not suitable for opioid therapy or identify those who need increased vigilance or monitoring during therapy.”⁴⁶⁹
- iv. Chou *et al.*, in reviewing four studies that evaluated the accuracy of risk assessment instruments, found that three studies reported “inconsistent results” for the 10-item Opioid Risk Tool No study evaluated the effectiveness of risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse.”⁴⁷⁰
- v. Indeed the Opioid Risk Tool, which was touted by Defendants for screening patients who could “safely” be prescribed opioids, has recently been invalidated. “In this population, we were not able to replicate the findings of the initial ORT study. Self-report was *no*

⁴⁶⁸ Weisner CM, Campbell CI, Ray GT, *et al.* Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. *Pain*. 2009;145(3):287-293, p. 292.

⁴⁶⁹ Kaye A, Jones M, Kaye A, *et al.* No Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1. Title. *Pain Physician J*. 2017, at p. 573. This conclusion was reaffirmed in a very recent review that concluded: “Despite their widespread use, most screening tools involving combinations of questions were based on low-quality studies or, when diagnostic performance was assessed among high-quality studies, demonstrated poor performance in helping to identify patients at high vs low risk.” Klimas, *et al.*, Strategies to Identify Patient Risks of Prescription Opioid Addiction When Initiating Opioids for Pain: A Systematic Review. *JAMA Netw Open*. 2019;2(5):e193365. doi:10.1001/jamanetworkopen.2019.3365.

⁴⁷⁰ Chou, *et al.*, “Effectiveness and Risks – Systemic,” fn. 204, above, at p. 280.

better than chance in predicting those who would have an opioid aberrant behavior. The ORT risk variables did not predict aberrant behaviors in either gender group. There was significant disparity in the scores between self-reported ORT and the ORT supplemented with medical record data (enhanced ORT).⁴⁷¹

- vi. There is a potential risk of any opioid risk tool: that prescribers gain a false sense of knowing who can and cannot get addicted, when in fact the biggest predictors of opioid dependency and addiction are access to opioids in the first place, and dose and duration, not personal characteristics. Indeed this focus on risky patients, rather than the inherent risk associated with opioids themselves, has been prevalent among prescribers in the 1980's, 1990's, and 2000's who were encouraged by the Defendants to rely on such tools, and it is in part responsible for the opioid epidemic we face today. Prescribers were incorrectly taught that by screening out high risk patients, they would avoid opioid misuse and addiction. For example, Janssen also promoted the concept that "the potential for addiction is in the patient, not the opioid" and defined high risk as "long-term exposure to opioids in addicts."⁴⁷² Both of these statements are false and misleading: opioids are inherently addictive and long-term exposure is a significant risk factor even in patients without other risk factors for addiction. Also, as discussed in this Report, abundant scientific literature demonstrates that even short-term exposure will result in chronic use and its attendant problems of addiction and dependence in a significant subset of patients.
- vii. The impact of the dose-duration risks of prescribed opioids will be felt for years, as evidenced by a recent study of OUD among hospitalized chronic pain patients which found that "prevalence of OUD increased substantially from 2011 to 2015...increas[ing] from 109,222 in 2011 to 172,680 in 2015 ($P < 0.001$)".⁴⁷³ As

⁴⁷¹ Clark, *et al.*, Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population, *Pain Med.* 2018 Feb 2. doi: 10.1093/pmt/pnx332. at p. 1382 (emphasis added).

⁴⁷² JAN-MS-00310473, produced in native at *11-12.

⁴⁷³ Orhurhu V et al. Trends of opioid use disorder among hospitalized patients with chronic pain. *Pain Practice.* 2019;19(6): 656-663, at p. 656.

patients are exposed to opioids for longer durations, the risk for developing OUD rises.

- viii. Further, prescribers who relied on Pharmaceutical Opioid Industry statements regarding the great benefits and minimal risks of prescribing opioids for pain would also gain a false sense that there was little or no need for screening.
- ix. It is unlikely that asking patients about risk factors will ever be a suitable method of screening, as motivation to minimize or omit risk factors in pursuit of obtaining a specific type of drug will weigh heavily on the truthfulness and transparency of reporting (*See discussion of Fleming study, above*). As noted in a very recent JAMA review, “Despite their widespread use, most screening tools involving combinations of questions were based on low-quality studies or, when diagnostic performance was assessed among high-quality studies, demonstrated *poor performance in helping to identify patients at high vs low risk.*”⁴⁷⁴
- x. Finally, Defendants were well aware that primary care physicians (PCPs), had neither the skills nor the resources to effectively monitor their patients for the development of opioid misuse and addiction, but nonetheless targeted these providers to promote sales.
 - A. At a 2001 Scientific Advisory Board meeting for Janssen Duragesic, it was evident that Janssen was targeting front line providers, i.e. PCPs to promote Duragesic.⁴⁷⁵
 - B. At the same time and at the same meeting, Janssen and its advisors were well aware the PCPs were not adequately trained to track opioid misuse and addiction: “Physicians

⁴⁷⁴ Klimas, *et al.*, Strategies to Identify Patient Risks of Prescription Opioid Addiction When Initiating Opioids for Pain, A Systematic Review, *JAMA Netw Open*. 2019;2(5):e193365. doi:10.1001/jamanetworkopen.2019.3365, at p. 1.

⁴⁷⁵ JAN-MS-00481055

are writing more opioid prescriptions, but they do not know how to monitor patients.”⁴⁷⁶

- C. Janssen’s own advisors conceded that even with training, it is extremely difficult to tell which patients will develop an opioid misuse problem: “Preliminary findings show that information or impressions gained in the doctor-patient relationship cannot predict which patients will have a positive urine toxicology screen. Even urine tox screens may not be reliable as they vary, and some have low sensitivities to oxycodone and fentanyl.”⁴⁷⁷
- D. Yet despite these tangible and openly recognized limitations, Defendants launched an aggressive marketing campaign targeting prescribers, which misrepresented the facts on risk of addiction and validity of screening, and instead aggressively promoted uptitration of their products.⁴⁷⁸

8. Increased supply of prescription opioids contributed substantially to more individuals becoming addicted to opioids and transitioning from prescription opioids to illicit sources of opioids such as heroin and fentanyl (The Gateway Effect).

- a. There is a clear causal link between prescription opioid exposure, prescription opioid misuse, and opioid addiction. Opioid misuse, or non-medical use of prescription opioids (NMUPO), is defined as taking an opioid medication outside of a prescribed indication.⁴⁷⁹ With increased opioid prescribing in the United States, more Americans have been exposed to prescription opioids at higher doses and for longer durations (including those not directly prescribed the opioid), contributing to rising incidence and prevalence of opioid misuse, dependence, addiction, and overdose death.⁴⁸⁰ These are the expected and natural consequences of exposing large populations to addictive and dangerous drugs, particularly

⁴⁷⁶ *Id.* at 1062.

⁴⁷⁷ *Id.* at 1064.

⁴⁷⁸ See JAN-MS-00779345, FDA Warning Letter to Janssen, RE: NDA #19-813, September 2, 2004.

⁴⁷⁹ NASEM Report (2017), fn. 42, above, at p. 152.

⁴⁸⁰ *Id.*, at p. 193

where tolerance requires users to increase the dose to achieve the same effect, resulting in ever-greater risk of harm.

- b. Teens are especially vulnerable to the increased access to prescription drugs. Adolescence is a time when the rapidly growing brain is more plastic, and therefore more vulnerable on a neurological level, to potentially irreversible brain changes caused by chronic drug exposure. Teens are also more likely to take risks, without appreciating the adverse consequences associated with those risks.⁴⁸¹
- c. In 2012, some 1.9 million individuals aged 12 or older misused a prescription drug for the first time within the past twelve months, an average of 1,350 initiatives per day. Prescription drugs now rank fourth among the most-misused substances in America, behind alcohol, tobacco, and marijuana. They rank second among teens. Of those who became addicted to any drug in the previous year, a quarter started out using a prescription medication: 17 percent began with opioid pain relievers, 5 percent with sedative-hypnotics, and 4 percent with stimulants.⁴⁸²
- d. In 2017, McCabe *et al.* found, “Adolescents who reported both medical and nonmedical use of prescription opioids were more likely to indicate medical use of prescription opioids before initiating nonmedical use...”⁴⁸³ “The findings provide compelling evidence that medical use of prescription opioids and NUPO are highly correlated, especially among adolescents. . . .We found that the majority of NUPO involved a history of medical use, and this finding should provide some concern to health professionals who prescribe opioid medications to adolescents, given the serious health consequences associated with NUPO.”⁴⁸⁴ McCabe’s references for this point include the Compton (2016) article (cited in 8.g.vi, below) that describes the trajectory from non-medical use to illicit opioids, thus emphasizing that McCabe is referring to the “Gateway Effect” transition, i.e., from initial medical use, to subsequent non-medical use, and ultimately to illicit opioids.

⁴⁸¹ Lembke, Drug Dealer MD, fn. 2, above, at pp. 26 and 48.

⁴⁸² *Id.*, at pp. 25-26.

⁴⁸³ McCabe, Sean Esteban, *et al.* Trends in medical and nonmedical use of prescription opioids among US adolescents: 1976–2015. *Pediatrics* 139.4 (2017): e20162387, at p. 1.

⁴⁸⁴ *Id.* at p. 8.

- e. McCabe *et al.* also conducted a subsequent prospective national study of high school seniors in the U.S. to identify the sequence of medical versus non-medical use of prescription opioids, and the later development of a substance use disorder (addiction). They found that almost one in every two high school seniors who reported the medical use of prescription opioids after initiating NMUPO had two or more substance use disorder (addiction) symptoms at age 35.⁴⁸⁵
 - i. These data show that teens who are exposed to prescription opioids without a prescription will often be further exposed through a subsequent medical prescription, and as a result are at increased risk of developing an opioid addiction later in life. The cumulative effect of prescription opioid exposure, through both medical and non-medical use, causally leads to opioid addiction.⁴⁸⁶
 - ii. The authors write, “These results indicate substantial risk for developing SUD among adolescents who have already initiated NMUPO and reinforce the critical role of screening when prescribing opioid analgesics to adolescents.”⁴⁸⁷ While the authors suggest that screening can play a role in mitigating future opioid addiction, screening tools have been shown to have limited efficacy in identifying at risk patients.⁴⁸⁸ The more significant goal is to reduce access to prescription opioids, which increases risk by increasing exposure to both medical and subsequent non-medical use.
- f. Writing in the journal *Pediatrics* (2018) Harbaugh *et al.* report that “The majority of US high school seniors with both medical use and nonmedical use of prescription opioids reported medical use before initiating nonmedical use of prescription opioids, suggesting a role of leftover

⁴⁸⁵ McCabe SE, Veliz PT, Boyd CJ, Schepis TS, McCabe V V., Schulenberg JE. A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife. *Drug Alcohol Depend.* 2019. doi:10.1016/j.drugalcdep.2018.10.027, at p. 379.

⁴⁸⁶ *Id.* at p. 381.

⁴⁸⁷ *Id.* at p. 383.

⁴⁸⁸ Clark MR, Hurley RW, Adams MCB. Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population. *Pain Med.* 2018;19(7):1382-1395. <http://dx.doi.org/10.1093/pmt/pnx332>, at p. 1382.

prescriptions in the transition to a nonmedical use of prescription opioids. This may be due, in part, to the perception that prescription opioids are safe if they are prescribed by physicians despite the fact that the addiction potential is similar to heroin.”⁴⁸⁹

- g. There is a clear causal link between prescription opioid exposure and the subsequent use of heroin and other illicit opioids.
 - i. The natural history of the disease of addiction is that individuals with addiction require increasing amounts and/or more potent forms over time to overcome tolerance, to maintain physiologic homeostasis, and to avoid painful withdrawal.
 - ii. As increasing numbers of Americans became addicted to prescription opioids over the past two decades, they were forced to seek out cheaper and more potent opioids. The illicit drug market met that increased demand with cheap and available heroin and fentanyl. Fentanyl, which is 50-100 times more potent than heroin and comes in white powder form similar to heroin, made its way into the illicit market without users realizing what they were ingesting, resulting in a surge of fentanyl related overdose deaths.
 - iii. “A preponderance of evidence suggests that the major increase in prescription opioid use beginning in the late 1990s has served as a gateway to increased heroin use⁴⁹⁰... The interrelated nature of the prescription and illicit opioid epidemics means that one cannot be addressed separately from the other.”⁴⁹¹
 - iv. In the 1960s, 80% of opioid users reported that their first exposure to opioids was in the form of heroin. By the 2000s, however, 75% of opioid users reported that their first exposure to opioids was in the form of prescription painkillers.⁴⁹²

⁴⁸⁹ Harbaugh CM, Lee JS, Hu HM, et al. Persistent Opioid Use Among Pediatric Patients After Surgery. *Pediatrics*. 2018;141(1):e20172439, at p. 5.

⁴⁹⁰ NASEM Report (2017) at fn. 42, above at p. 215.

⁴⁹¹ *Id.* at p. 248.

⁴⁹² Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the united states: A retrospective analysis of the past 50 years. *JAMA Psychiatry*. 2014. doi:10.1001/jamapsychiatry.2014.366, at p. E-1.

- v. In a study based on NSDUH data from 2002-2011, the incidence of heroin use among people who reported prior nonmedical use of prescription opioids was 19 times as high as the incidence among persons who reported no previous nonmedical use.⁴⁹³
- vi. Prescription opioid use disorder/addiction is associated with a likelihood of heroin addiction that is 40 times as great as the likelihood with no prescription-opioid misuse or addiction, even after accounting for sociodemographic, geographic, and other substance abuse or dependence characteristics.⁴⁹⁴
- vii. Eighty-six percent of urban people who used injected heroin in New York and Los Angeles in 2008 and 2009 had used prescription opioids nonmedically before using heroin.⁴⁹⁵ Similar studies conducted in San Diego, Seattle, and New York showed that 40%, 39%, and 70% of heroin users, respectively, reported that they had used prescription opioids nonmedically before initiating heroin use.⁴⁹⁶
- viii. Muhuri found that 79.5% of persons who recently began using heroin had used prescription opioids nonmedically before initiating heroin use.⁴⁹⁷
- ix. A study of heroin users in Wilmington, Delaware, found that “most reported that prescription opioids were indeed their gateway to heroin use.”⁴⁹⁸
- x. A 2014 research paper evaluating transitions from opioid pills to heroin injecting in Philadelphia and San Francisco, concluded that,

⁴⁹³ Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the united States. *CBHSQ Data Rev.* 2013;(August):1-16, at p. 1.

⁴⁹⁴ Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *N Engl J Med.* 2016. doi:10.1056/NEJMra1508490, at p. 157.

⁴⁹⁵ Lankenau SE, Teti M, Silva K, Bloom JJ, Harocopoulos A, Treese M. Initiation into prescription opioid misuse amongst young injection drug users. *Int J Drug Policy.* 2012;23(1):37-44, at p. 41.

⁴⁹⁶ Compton, *et al.*, “Relationship Between NPOU and Heroin Use,” fn. 494, above, at p. 156.

⁴⁹⁷ Muhuri, *et al.*, “Associations of NMPRU and Heroin,” fn. 493, above, at p. 1.

⁴⁹⁸ Inciardi JA, *et al.*, Prescription Opioid Abuse and Diversion in an Urban Community: The Results of an Ultra-Rapid Assessment. *Pain Medicine.* 2009;10:537-548, at p. 544.

“Unlike those substances previously labeled ‘gateway drugs’, opioid pills seem to have a direct relationship with progression to heroin initiation.”⁴⁹⁹

- xii. A recent article by Pielech, *et al.*, stated, “Emerging data indicate that *any* exposure to opioids as an adolescent (medical or non-medical) appears to present short and long term risks for initiating heroin and prescription opioid use.”⁵⁰⁰
- xiii. The number of Americans aged 12 and older with past month heroin use, rose from 281,000 to 335,000 between 2011 and 2013,⁵⁰¹ a significant increase from the 166,000 using heroin in 2002.
- xiv. In 2017, more than 28,000 deaths in the United States involved a synthetic opioid, primarily fentanyl, more deaths than from any other type of opioid.⁵⁰²
- h. The epidemic of prescription opioid misuse, addiction, and overdose death beginning in the 1990s has been a significant factor contributing to the subsequent increase in heroin and fentanyl misuse, addiction, and overdose death. Further, the Pharmaceutical Opioid Industry knew that prescription opioids are a gateway to illicit opioids. In March 2011, Purdue’s “Hair Testing Advisory Panel,” convened to help make the

⁴⁹⁹ Mars SG, *et al.*, “Every ‘Never’ I Said Came True”: Transitions from Opioid Pills to Heroin Injecting. *Int'l J. of Drug Policy*. 2014;25:257-266, at p. 264

⁵⁰⁰ Pielech, *et al.*, Receipt of Multiple Outpatient Prescriptions Is Associated With Increased Risk of Adverse Outcomes in Youth: Opioid Prescribing Trends, Individual Characteristics, and Outcomes from 2005-2016. *PAIN* 2020, published ahead of print. DOI:10.1097/j.pain.0000000000001812, at p. 2 (emphasis in original).

⁵⁰¹ McCarthy M. Illicit drug use in the US holds steady, but heroin use is on rise. *BMJ*. 2013;347(September):f5544. doi:10.1136/bmj.f5544, at p. 1.

⁵⁰² Cts. for Disease Control and Prevention. *Synthetic Opioid Overdose Data*, (Apr. 2, 2019) <https://www.cdc.gov/drugoverdose/data/fentanyl.html>.

argument in favor of OxyContin’s “tamper-resistant formulation,” concluded that one of the “anticipated impacts of reformulation” was “reducing *OxyContin’s role as a gateway drug*” for recreational users.⁵⁰³

9. Increased supply of prescription opioids contributed substantially to more individuals, including newborns, becoming dependent on opioids, increasing their risk for opioid-related morbidity and mortality (The Dependence Effect).

- a. Prescription opioids induce physiological dependence almost universally, and dependence leads to addiction in a significant subset of users, particularly as dose and duration of exposure are increased.
- b. Over the last 30 years, the liberal prescribing of opioids for chronic pain has created a “legacy” population of patients who have been on opioids for several years if not decades, and are now physically dependent on opioids, making it difficult to come off (The Dependence Effect).
- c. Physiologic dependence, as currently defined by the DSM-5, is not the same as addiction. Dependence is the process whereby the body comes to rely on the drug to maintain biochemical equilibrium. When the drug is not available at expected doses or time intervals, the body becomes biochemically dysregulated, which manifests as the signs and symptoms of withdrawal. Although opioid dependence as currently defined is not the same as addiction, dependence on opioids can be associated with significant morbidity and mortality, and thus is not the same thing as dependence on other medications used as evidence-based treatment for illness.⁵⁰⁴ Also, while dependence is defined differently from addiction, the line between them is not well-defined; in particular, the evidence of addiction often comes when an opioid-dependent patient attempts to taper and discovers that the loss of the drug causes the craving and compulsion that define addiction. In my clinical experience, dependence in some individuals can develop quickly. This clinical experience is consistent with studies showing that even short-term prescriptions of opioids for acute injuries result in long-term use of opioids after the acute condition has passed.⁵⁰⁵ In the DSM-4, the edition prior to the DSM-5, “opioid use

⁵⁰³ PPLP003370086 at 0106 (emphasis added).

⁵⁰⁴ Lembke, *et al.*, “Weighing the Risks,” fn. 4, above.

⁵⁰⁵ Delgado M, *et al.* National Variation in Opioid Prescribing and Risk of Prolonged Use for Opioid-Naive Patients Treated in the Emergency Department for Ankle Sprains. *Ann Emerg Med.* 2018, at p. 1; see also Howard R, Fry B,

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disorder” was called “opioid dependence.” The new DSM-5 criteria made it more difficult to diagnose Opioid Use Disorder (opioid addiction), by removing the criteria of withdrawal and tolerance from the definition in the case of a patient taking prescribed opioids under a doctor’s care. The DSM-5 thereby reduced the proportion of patients who could be diagnosed with opioid use disorder.

- d. By 2005, long-term opioid therapy was being prescribed to approximately 10 million Americans. “In 2014 alone, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers. Of these prescriptions, 65% were for short-term therapy (<3 weeks), but 3 to 4% of the adult population (9.6 million to 11.5 million persons) were prescribed longer-term opioid therapy.”⁵⁰⁶
- e. Once established, opioid dependence represents a complex, debilitating, and sometime irreversible clinical problem. In some cases, the suffering from withdrawal is so extreme that patients say they would rather die than go through it. Indeed people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.
- f. Opioids cause neuroadaptation⁵⁰⁷ and lead to tolerance, physiologic dependence, and painful withdrawal, even without the more complex biopsychosocial disease of addiction. As such, tolerance, dependence, and withdrawal in and of themselves represent real harm to patients as a result of opioid therapy. Due to tolerance, dependence, and withdrawal, many patients taking prescription opioids today will require an enormous investment of resources to help them get off of opioids or onto lower, safer doses.
- g. Withdrawal refers to the physiologic manifestations of not having the substance, the symptoms of which vary from substance to substance. As a general albeit oversimplified principle, the characteristics of withdrawal from a given substance are the opposite of intoxication for that substance. Withdrawal from opioids includes dysphoria (unhappiness), anxiety,

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Gunaseelan V, et al. Association of Opioid Prescribing with Opioid Consumption after Surgery in Michigan. *JAMA Surgery*. 2018, at p. E-6.

⁵⁰⁶ Volkow, et al., “Misconceptions and Mitigation,” fn. 35, above, at p. 1253.

⁵⁰⁷ Koob, “Neurocircuitry”, fn. 31, above, at p. 217.

insomnia, agitation, restlessness, muscle fasciculations, increased heart rate, elevated blood pressure, diarrhea, nausea, vomiting, and body pain. Although opioid withdrawal is generally thought to be painful but not life threatening, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.⁵⁰⁸

- h. Clinical experience and clinical studies demonstrate that the majority of opioid legacy chronic pain patients (that is, patients who have been taking opioids daily for months to years) are physiologically dependent on opioids and struggle to taper, even when opioids pose imminent risk.
 - i. In a study at Oregon Health & Sciences University, after a hospital and clinic wide policy was implemented to get high dose legacy patients' doses down below 120 MED per day, including intensive physician education from 2011 to 2013,⁵⁰⁹ 71 (63%) continued high-dose opioids in the post-intervention period.⁵¹⁰ In other words, even with a hospital wide initiative, a minority of patients tapered to safer doses.
 - ii. In a Danish study in which subjects were tapered off of opioids by reducing by 10% of the daily opioid dose every week until discontinuation,⁵¹¹ only 13 of 35 patients randomized to the opioid taper completed the study without dropping out. The authors wrote "Although our study is hampered by a vast dropout rate, we still feel that it is highly justified to point to the fact that the stabilization of opioid treatment is not a simple task and opioid tapering off seems to be extremely difficult in CNCP patients in general"⁵¹²

⁵⁰⁸ Stark MM, Payne-James J. People can die from opiate withdrawal. *Med Sci Law*. 2017;57(2):103. doi:10.1177/0025802417704600 at p. 103; see also Bohnert ASB, Ilgen MA. Understanding Links among Opioid Use, Overdose, and Suicide. *N Engl J Med*. 2019. doi:10.1056/nejmra1802148, at p. 77.

⁵⁰⁹ Weimer MB, Hartung DM, Ahmed S, Nicolaïdis C. A chronic opioid therapy dose reduction policy in primary care. *Subst Abus*. 2016;37(1):141-147, at pp. 141-142.

⁵¹⁰ *Id.* at p. 114.

⁵¹¹ Kurita GP, Højsted J, Sjøgren P. Tapering off long-term opioid therapy in chronic non-cancer pain patients: A randomized clinical trial. *Eur J Pain*. 2018;22(8):1528-1543, at p. 1531.

⁵¹² *Id.* at p. 1536.

- i. On May 18, 2006, Purdue's David Haddox received the "excellent news" from Sidney Scholl, of Pinney Associates, that "Chuck O'Brien will be heading up the SUD [Substance Use Disorder] section of the DSM-V. This means that there is a good chance that 'addiction' will replace 'dependence' and there can be some changes in the diagnostic criteria that will reflect issues related to abuse and addiction of prescription opioids. Chuck asked me to assist him in this process. I would appreciate your input in this process. ... If Marc Schuckit, who was originally slated to head up the SUD section, was still in charge, we would not be in this position as he likes the use of dependence over addiction. This is an opportunity we should not overlook, as major revisions of the DSM do not occur very often." Haddox wrote back, "This is really good news, Sid."⁵¹³
- j. On March 24, 2008, Haddox wrote to Phillip Lippe in response to Lippe's request for comments regarding the American Medical Association's Report on Substance Abuse. Haddox wrote, "I am glad to see AMA getting into this area. Certainly the definitions and diagnostic criteria need some work...we are all fortunate that Charles O'Brien is the head of the substance use disorders section."⁵¹⁴
- k. On November 6, 2008, Haddox wrote to Chuck O'Brien, "It was good to see you this past weekend at ICPCD [International Conference on Pain and Chemical Dependency]. I really am excited that you are educating your nonclinical colleagues about the need for diagnostic nomenclature that are applicable in the real (read: clinical) world." Haddox went on to ask O'Brien to consult on a tamper-resistant opioid analgesic work group, and referenced prior payment of \$2400 at O'Brien's rate of \$600 per hour, "when it was anticipated that you would accompany us to the FDA Advisory Committee in March." Haddox added, "Also, in the interest of public health and medicine, I don't want to do anything to impair your ability to complete your DSM-V duties." O'Brien wrote back on November 12, 2008, to "Dave, I would be very happy to do this but it would simplify my life with Penn if we could consider this activity an extension [of] my efforts of several months ago where I already signed a

⁵¹³ PPLP004058443.

⁵¹⁴ PPLPC031000425439.

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contract.” Haddox replied that he was “really pleased that you will be able to work with us on this.”⁵¹⁵

- 1. On March 25, 2008, Haddox again exchanged emails with Philipp Lippe. Dr. Lippe expressed concern that under DSM-IV, the first three criteria for diagnosis of substance dependence “are inherent in pain management,” that is, “(1. Tolerance; (2) withdrawal symptoms; and (3) increased dosage or length of use.” Haddox wrote to Lippe, “I have great confidence that the DSM-V will improve on this language, based on the chair of the SUD [committee].”⁵¹⁶
- m. Dr. O’Brien’s consulting and financial relationship with Purdue goes back to at least 2003.⁵¹⁷ Through 2006, Dr. O’Brien appeared as an expert witness for Purdue in at least 9 cases in the federal courts of Florida,⁵¹⁸ Missouri, Ohio, Texas, Georgia and Illinois and Texas state court providing opinions that plaintiffs were not addicted, and not injured by dependence, which was described as an “expected consequence” of taking OxyContin and easily resolved by tapering.⁵¹⁹ In the Savant v. Purdue case in 2005, Dr. O’Brien’s report stated that he was compensated at the rate of \$550 per hour.⁵²⁰ O’Brien signed a consulting agreement with Purdue, effective from April 2008-April 2013,⁵²¹ essentially contemporaneous with his tenure as Chair of the DSM-5 Substance Abuse

⁵¹⁵ PPLPC018000252189 at 2190-2191.

⁵¹⁶ PPLPC018000201219 at 1219-1222.

⁵¹⁷ Dr. O’Brien testified that since 1969, he has been a paid consultant to numerous pharmaceutical/opioid manufacturers including McNeil, Janssen, Johnson & Johnson, Cephalon, Purdue and others. O’Brien also testified that he “helped them [McNeil] decide to purchase Tramadol from a German company and help them get that started.” Timmons v Purdue Pharma (2005) Deposition of Charles P. O’Brien, produced at PKY183320282 at PKY183320393-0394.

⁵¹⁸ Timmons v Purdue Pharma et al. No. 8:04-CV-1479-T-26MAP (M.D. Fla., 2005) produced at PKY183320282; Savant v Purdue Pharma et al., No. 04-394-DRH, 2005 WL 6503987 (S.D.Ill. 2005); Taylor v Purdue Pharma et al., No. 504-CV-197, 2005 WL 3308504 (M.D. Georgia 2005); McKnight v Purdue Pharma et al., No. 9:04 Civ-116, 2005 WL 5794391 (E.D.Texas 2005); Harris v Purdue Pharma et al., No. C-1-01-428, 2004 WL 4012101 (S.D. Ohio 2004); Branch v Purdue Pharma et al. No. LR 1696-3, 2004 WL 3752789 (Tex. Dist. Richmond Civil); Campbell v Purdue Pharma et al, No. 1:02CV00163TCM, 2004 WL 6057307 (E.D. Missouri 2004); Labzda v Purdue Pharma et al, No. 01-8726-CIV-FERGUSONSNOW, 2003 WL 26100920 (S.D. Fla. 2003); Williams v Purdue Pharma et al. No. 4:04CV02407 (S.D. Texas 2006), produced at PKY182921037

⁵¹⁹ Harris, 2004 WL 4012101, at *5.

⁵²⁰ Savant, 2005 WL 6503987, at *9.

⁵²¹ PPLP003478540

working group, from 2007-2013.⁵²² Remarkably, in 2013, O'Brien disclosed no financial relationship to Purdue or any other party as a co-author and Chair of the group that published the rationale for the changes to the new DSM-5 section on substance abuse.⁵²³

- n. This sequence of events indicates that Purdue's consultant, O'Brien, who was on a first name basis with Haddox, was responsible for the work that altered the DSM-5 definition of opioid use disorder in a manner that suited Purdue's goals by distinguishing between "dependence" on the one hand, and "use disorder" or "addiction" on the other. This history is consistent with a larger effort on the part of Purdue and other opioid manufacturers to characterize dependence as a benign condition entirely separate from addiction. In reality, dependence, withdrawal, and tolerance, are closely linked to the disease of addiction, and from a neurobiological perspective, may be identical phenomena. Further, by excluding the criteria of tolerance and withdrawal, and by completely removing dependence from the diagnostic criteria, the DSM-5 raised the threshold for diagnosing OUD in this vulnerable population, consisting of approximately 20-30% of long-term opioid users who progressed to OUD.⁵²⁴ As a result of making it more difficult to diagnose OUD, some of these patients were denied the benefits of timely, evidence-based treatment of their conditions.
- o. Regardless of these changing and disparate definitions, the bottom line has not changed: prescription opioids induce physiological dependence almost universally, and result in addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Both represent significant harms.
- p. Even limited exposure to opioids through a doctor's prescription, can lead to persistent opioid use. In other words, once patients start opioids, they are at significant risk to continue them beyond the time of injury, *i.e.* to become dependent on them.

⁵²² Hasin DS, O'Brien CP *et al.* DSM-5 Criteria for Substance Use Disorders: recommendations and rationale. *Am J Psychiatry* 2013;170(8):834-851. at p.2,
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3767415/pdf/nihms515995.pdf>,

⁵²³ *Id.*, at pp. 1 and 12.

⁵²⁴ Vowles, "Rates of Opioid Misuse", fn. 290, above, discussed above at §C.7.b.

- i. Brummett *et al.* sought to determine the incidence of new persistent opioid use after minor and major surgical procedures. Using a nationwide insurance claims data set from 2013 to 2014, they calculated the incidence of persistent opioid use for more than 90 days among opioid-naïve patients after both minor and major surgical procedures. The authors found the rates of new persistent opioid use were similar between the two groups, ranging from 5.9% to 6.5%. By comparison, the incidence in the nonoperative control cohort was only 0.4%. The authors wrote, “New persistent opioid use represents a common but previously underappreciated surgical complication that warrants increased awareness.”⁵²⁵ The more opioids prescribed after surgery, the more patients tend to use. The number of opioid pain pills prescribed after surgery is a bigger predictor of how many opioids the patient will use, than is self-reported pain.
- ii. A study by Delgado *et al.* looked at opioid naïve patients being treated for a common minor injury, ankle sprain, in the emergency department (ED) to determine the association between initial opioid prescription intensity and transition to prolonged opioid use. The authors concluded that opioid prescribing for ED patients treated for ankle sprains is “common,” and prescriptions greater than 225 MED were associated with approximately five times higher rates of prolonged opioid use than with lower MED exposure. As the authors stated, “This is concerning because these prescriptions could still fall within 5- or 7-day supply limit policies aimed at promoting safer opioid prescribing.”⁵²⁶
- iii. A very recent 2020 retrospective cohort study of 259,115 opioid naïve adult patients undergoing endocrine surgery found the rate of new persistent opioid use [ie, receipt of 1 or more opioid prescriptions 90-180 days postop with no intervening procedures] was 7.4% but that “[i]mportantly, the risk for persistent opioid use

⁵²⁵ Brummett CM, Waljee JF, Goesling J, *et al.* New persistent opioid use after minor and major surgical procedures in us adults. *JAMA Surg.* 2017., at p. 1.

⁵²⁶ Delgado, *et al.*, “National Variation,” fn. 505, above, at p. 1

- increased with higher doses of total amount of opioids prescribed.”⁵²⁷
- iv. Numerous other studies have been published in the last three years showing persistent opioid use 3-12 months after even minor surgeries in opioid naïve patients: (10%⁵²⁸; 10%⁵²⁹; 5%⁵³⁰; 13%⁵³¹; 13%⁵³²; 8%⁵³³; 10%-13%⁵³⁴)
 - q. Conversely, the fewer opioids prescribed in the weeks and months following surgery, the less likely patients are to become persistent opioid users.⁵³⁵ When opioids are restricted, patients do not tend to experience more pain, less satisfaction, or call in more frequently for refills.⁵³⁶

⁵²⁷ Kuo JH, et al. Use and Misuse of Opioids after Endocrine Surgery Operations. *Annals of Surgery*. 2020;1-6, at p. 1.

⁵²⁸ Marcusa DP et al. Prescription Opioid Abuse among Opioid-Naïve Women Undergoing Immediate Breast Reconstruction. *Plast Reconstr Surg*. 2017 Dec;140(6):1081-1090. doi: 10.1097/PRS.0000000000003832, at p. 1081.

⁵²⁹ Lee JS et al. New Persistent Opioid Use Among Patients with Cancer after Curative-Intent Surgery. *J Clin Oncol*. 2017 Dec 20;35(36):4042-4049. doi: 10.1200/JCO.2017.74.1363, at p. 4042.

⁵³⁰ Harbaugh, et al., “Persistent Opioid Use”, fn. 489, above, at p. 1.

⁵³¹ Deyo RA et al. Use of Prescription Opioids Before and After an Operation for Chronic Pain (lumber fusion surgery). *Pain*. 2018 Jun;159(6):1147-1154. doi: 10.1097/j.pain.0000000000001202, at p. 5.

⁵³² Johnson SP et al. Risk of Prolonged Opioid Use Among Opioid-Naïve Patients Following Common Hand Surgery Procedures. *J Hand Surg Am*. 2016 Oct;41(10):947-957.e3. doi: 10.1016/j.jhsa.2016.07.113, at p. 947.

⁵³³ Goesling J et al. Trends and Predictors of Opioid Use After Total Knee and Total Hip Arthroplasty. *Pain*. 2016 Jun;157(6):1259-65. doi: 10.1097/j.pain.0000000000000516, at p. 1259.

⁵³⁴ Cook DJ et al. Benchmarks of Duration and Magnitude of Opioid Consumption After Total Hip and Knee Arthroplasty: a database analysis of 69,368 patients. *J. Arthroplasty*. 2019; 34: 638-644, at p. 638.

⁵³⁵ Brummett, “New Persistent Opioid Use”, fn. 525, above; Gil JA, et al. Risk of Prolonged Opioid Use Among Opioid-Naïve Patients After Common Shoulder Arthroscopy Procedures. *Am J Sports Med* 2019; 47(5); 1043-1050, at p. 1049; Larach DB, Sahara MJ, et al. Patient Factors Associated with Opioid Consumption in the Month Following Major Surgery. *Ann Surg*. 2019; 1-9, at p. 1.

⁵³⁶ Bateman BT, Cole NM, et al. Patterns of opioid prescription and use after cesarean delivery. *Obstet Gyn*. 2017; 130(1): 1-17, at p. 3; Howard R, et al. Reduction in opioid prescribing through evidence-based prescribing guidelines. *JAMA Surg* 2018; 153(3): 285-287, at p. 287; Lee JS, Hu HM, Brummett CM, et al. Postoperative Opioid Prescribing and the Pain Scores on Hospital Consumer Assessment of Healthcare Providers and Systems Survey. *JAMA*. 2017;317(19):2013–2015, at p. 2014; Sekhri S, Arora NS, et al. Probability of opioid prescription refilling after surgery: does initial prescription dose matter? *Ann Surg*. 2018; 268(2): 271-276, at p. 275.

- r. A recent NASEM Report addresses the role of opioid prescribing for acute pain, including surgical and other contexts, as a contributing factor to the epidemic of abuse, overdose and mortality.⁵³⁷ The Report confirms the increasing awareness that opioids are overprescribed even for acute pain, and that an important subset of acute pain patients go on to long-term use of prescription opioids and the risks that accompany such use.⁵³⁸
- s. Just as increased exposure has been the cause of increased consumption and risk,⁵³⁹ decreasing exposure decreases opioid consumption and risk. When doctors initiate fewer opioids, patients consume fewer opioids, without increases in pain. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment, while at the same time reducing the risk of diversion of unused pills to unauthorized users. Recent studies in a wide range of medical conditions have consistently demonstrated that patients' experience of pain is not increased when opioids are reduced or eliminated from treatment protocols. Examples of research are summarized below.
 - i. In a study in which patients were treated with Tylenol/ibuprofen after parathyroid and thyroid surgery, the authors concluded that such patients "need very little, if any, post-operative opioids.... Decreasing the volume of opioid medications prescribed at discharge will decrease waste and reduce potential for addiction."⁵⁴⁰

⁵³⁷ National Academies of Sciences, Engineering, and Medicine (NASEM 2020). 2020. *Framing Opioid Prescribing Guidelines for Acute Pain: Developing the Evidence*. Washington, DC: The National Academies Press..<https://www.nap.edu/catalog/25555/framing-opioid-prescribing-guidelines-for-acute-pain-developing-the-evidence>

⁵³⁸ *Id.*, at p. 1. A further, very recent publication adds to this evidence: among women who took prescription opioids for acute pain after childbirth, there was an increased risk of Serious Opioid-Related Events (a composite consisting of persistent opioid use, opioid use disorder diagnosis, methadone or buprenorphine prescription, opioid overdose diagnosis, and opioid-related death) compared with women who did not take opioids after childbirth, and the risk increased with more post-partum opioid prescriptions. Osmundson SS, *et al.*, Opioid prescribing after childbirth and risk for serious opioid-related events: a cohort study. *Annals of Internal Medicine* 2020; doi:107326/M19-3805, at p. 2.

⁵³⁹ Howard, *et al.*, "Association of Opioid Prescribing," fn. 505, above, at p. E6.

⁵⁴⁰ Shindo M, Lim J, Leon E, Moneta L, Li R, Quintinalla-Diek L. Opioid Prescribing Practice and Needs in Thyroid and Parathyroid Surgery. *JAMA Otolaryngology - Head and Neck Surgery*. 2018, at p. 1102.

- ii. A case-control cohort study of 1,231 patients undergoing gynecologic oncology surgery, implemented an “ultrarestrictive opioid prescription protocol” (UROPP), resulting in a significant decrease in the number of opioids dispensed during the entire perioperative period, without changes in postoperative pain scores, complications, or increases in the number of refill requests.⁵⁴¹
- iii. The authors write, “For patients who underwent laparoscopic or robotic surgery, the mean (SD standard deviation) number of opioid tablets given at discharge was 38.4 (17.4) before implementation of the UROPP and 1.3 (3.7) after implementation ($P < .001$). After ambulatory surgery, the mean (SD) number of opioid tablets given at discharge was 13.9 (16.6) before implementation of the UROPP and 0.2 (2.1) after implementation ($P < .001$). The mean (SD) perioperative oral morphine equivalent dose was reduced to 64.3 (207.2) mg from 339.4 (674.4) mg the year prior for all opioid-naïve patients ($P < .001$).”⁵⁴²
- iv. “The significant reduction in the number of dispensed opioids was not associated with an increase in the number of refill requests (104 patients [16.6%] in the pre-UROPP group vs 100 patients [16.5%] in the post-UROPP group; $P = .99$), the mean (SD) postoperative visit pain scores (1.1 [2.2] for the post-UROPP group vs 1.4 [2.3] for pre-UROPP group; $P = .06$), or the number of complications (29 cases [4.8%] in the post-UROPP group vs 42 cases [6.7%] in the pre-UROPP group; $P = .15$).”⁵⁴³
- v. Similarly, non-opioids have been found equivalent to opioids for relief of pain treated in emergency departments. “For adult ED [Emergency Department] patients with acute extremity pain, there were no clinically important differences in pain reduction at 2 hours with ibuprofen and acetaminophen or 3 different opioid and

⁵⁴¹ Mark J, Argentieri DM, Gutierrez CA, *et al.* Ultrarestrictive Opioid Prescription Protocol for Pain Management After Gynecologic and Abdominal Surgery. *JAMA Netw Open*. 2018;1(8):e185452. doi:10.1001/jamanetworkopen.2018.5452.

⁵⁴² *Id.* at p. 1.

⁵⁴³ *Id.* at pp. 1-2.

acetaminophen combination analgesics.”⁵⁴⁴ Based on data from 2006-2010, opioids were prescribed for 18.7% of ED discharges; yet “[t]he findings support the inference that there are no clinically meaningful differences between the analgesic effects of these 4 analgesics and suggest that a combination of ibuprofen and acetaminophen represents an alternative to oral opioid analgesics for the treatment of acute extremity pain in the ED.”⁵⁴⁵

- t. In most cases, opioid dependent patients require a protracted medically supervised taper to lower their doses. I have worked with others to develop a protocol for safely and compassionately tapering opioid-dependent patients to lower doses or to eliminate them entirely. See discussion of the “BRAVO Protocol” and my recent publication on patient-centered tapering, below. Studies show that pain in the majority of patients *improves* when patients on chronic high dose opioid therapy reduce their dose or come off of opioids.
- u. It is inhumane to abruptly discontinue opioids in patients who have become dependent through a medical prescription.⁵⁴⁶ The preferred approach is a slow and compassionate taper⁵⁴⁷ when risks outweigh the benefits.
- v. A retrospective research study of patients consecutively admitted to the Mayo Clinic Pain Rehabilitation Center from 2006 through 2012, with a pain diagnosis of fibromyalgia, showed that patients tapered off of opioids had significant improvements in pain-related measures including numeric pain scores and functionality.⁵⁴⁸

⁵⁴⁴ Chang AK, et al. Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. *JAMA*. 2017;318(17):1661–1667.
doi:10.1001/jama.2017.16190, at p.1661.

⁵⁴⁵ *Id.*

⁵⁴⁶ United States Department of Health and Human Services. *HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-term Opioid Analgesics*. (Oct. 2019); https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf.

⁵⁴⁷ *Id.* at p. 3, opioid tapering flowchart based on Oregon Pain Guidance BRAVO protocol.

⁵⁴⁸ Cunningham JL, Evans MM, King SM, Gehin JM, Loukianova LL. Opioid tapering in fibromyalgia patients: Experience from an interdisciplinary pain rehabilitation program. *Pain Med* (United States). 2016.
doi:10.1093/pmt/pnv079, at p. 1676.

- w. A meta-analysis of opioid legacy patients (patients on long-term opioid therapy as a “legacy” of opioid prescribing in the 1990s) demonstrated that pain improves for many patients who decrease or go off of long-term opioid therapy (LTOT). Sixty-seven studies were included in this analysis. Among 40 studies examining patient outcomes after dose reduction, improvement was reported in pain severity (8 of 8 fair-quality studies), function (5 of 5 fair-quality studies), and quality of life (3 of 3 fair-quality studies).⁵⁴⁹ The authors repeatedly note the need for more research and better quality evidence. Nonetheless, the authors concluded, “this systematic review suggests that pain, function and quality of life may improve during and after opioid dose reduction.”⁵⁵⁰
- x. In a study by Sullivan *et al.*, high dose legacy patients were randomly assigned to a 22-week taper support intervention (psychiatric consultation, opioid dose tapering, and 18 weekly meetings with a physician assistant to explore motivation for tapering and learn pain self-management skills) or usual care (N=35).⁵⁵¹ The authors write, “It is important to note that the opioid dose reduction in both the taper support and usual care groups was achieved without a significant increase in pain severity. In fact, pain severity decreased on average from baseline to 22 weeks by approximately 1 point on the 0–10 scale in the taper support group and approximately a half-point in the usual care group. This finding is consistent with those in studies of inpatient pain rehabilitation programs, which have documented pain reduction with opioid dose reduction.”⁵⁵²
- y. A small outpatient study of opioid tapering in community patients showed no increase in pain intensity scores in patients who were able to taper their opioids by greater than 50% from the starting dose. The median opioid dose in the sample was 288 MED. The median duration of opioids was six years. Median pain intensity was moderate (5 out of 10 on a numeric pain rating). After four months, the median MED was reduced to 150 (IQR, 54–

⁵⁴⁹ Frank JW, Lovejoy TI, Becker WC, *et al.* Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: A systematic review. *Ann Intern Med.* 2017;167(3):181-191. doi:10.7326/M17-0598, at pp. 185-186.

⁵⁵⁰ *Id.* at p. 186.

⁵⁵¹ Sullivan MD, Turner JA, DiLodovico C, D’Appollonio A, Stephens K, Chan Y-F. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. *J Pain.* 2017. doi:10.1016/j.jpain.2016.11.003, at p. 308.

⁵⁵² *Id.* at p. 318.

248) mg (P = .002). Of note, neither pain intensity (P = .29) nor pain interference (P = .44) increased with opioid reduction.⁵⁵³

- z. Many patients on chronic opioid therapy are reluctant to taper. In addition, some physicians and authors question whether tapering is necessary if the patient is stable and adherent to their current dose. Yet it is well established that patients on high doses of opioids are at increased risk for a variety of side effects, serious morbidities, and death.⁵⁵⁴ Quality of life may be adversely affected, despite the fact that the patient perceives benefit in terms of pain relief. Indeed, as above, data show that in addition to reducing opioid-related risk, pain can improve when patients lower their opioids, which is evidence in and of itself that opioids do not work for chronic pain for those patients.
- aa. A newborn is born dependent on opioids as a result of being exposed to opioids *in utero*. According to DSM-5 criteria, the opioid dependent newborn is not “addicted,” because addiction requires the manifestations of certain pathological and maladaptive behaviors in conjunction with opioid use. The newborn is the passive recipient of opioids due to the mother’s exposure.
 - i. The rate of admission to neonatal intensive care units (“NICU”) for neonatal abstinence syndrome (“NAS”), a drug-withdrawal syndrome that occurs after *in utero* exposure to opioids, increased from 7 cases per 1000 admissions to 27 cases per 1000 admissions between 2004 and 2013.⁵⁵⁵
 - ii. Tolia reported that “the median length of stay increased from 13 days to 19 days (P<0.001 for both trends). The total percentage of NICU [neonatal intensive care unit] days nationwide that were

⁵⁵³ Darnall BD, Ziadni MS, Stieg RL, Mackey IG, Kao MC, Flood P. Patient-centered prescription opioid tapering in community outpatients with chronic pain. *JAMA Intern Med.* 2018. doi:10.1001/jamainternmed.2017.8709, at p. 708.

⁵⁵⁴ Gomes T, Mamdani MM, Dhalla Ia, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med.* 2011;171(7):686-691. doi:10.1001/archinternmed.2011.117, at p. 686; *see also* Lembke *et al.*, Weighing The Risks,” fn. 4, above, at p. 982; Edlund *et al.*, Role of Opioid Prescription,” fn. 59, above, at p. 7; Chou *et al.*, “Effectiveness and Risks,” fn. 204, above, at p. ES-1.

⁵⁵⁵ Tolia VN, Patrick SW, Bennett MM, *et al.* Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *Obstet Gynecol Surv.* 2015. doi:10.1097/OGX.0000000000000243, at p. 2118.

attributed to the neonatal abstinence syndrome increased from 0.6% to 4.0% (P<0.001 for trend), with eight centers reporting that more than 20% of all NICU days were attributed to the care of these infants in 2013.”⁵⁵⁶

- iii. This approximate quadrupling of the rate of NAS is directly attributable to the epidemic of opioid use disorder that began with promotion of prescription opioids and continues to the present, accompanied by use of illicit opioid drugs. A recent article reports, “Neonatal abstinence syndrome (NAS) is seen at a very high rate at our institution in Huntington, West Virginia,” and a table of commonly identified drug combinations all include opioids (“Opioid and gabapentin,” “Opioid and THC,” “Opioid and benzodiazepine,” “Opioid and Nicotine,” “Opioid and nicotine/caffeine.”)⁵⁵⁷ As noted previously, prescription opioids alone were most common among patients who overdosed during the period from 1999-2002, before users transitioned to heroin and fentanyl, And the same was true in Cabell County based on the available data starting in 2001.⁵⁵⁸

- bb. Defendants’ promotional documents conveyed the message that prescription opioid dependence is not a significant concern, and that patients can be easily tapered off their prescriptions in a brief period of time. That message is contradicted by the scientific literature, my own clinical experience, and patients’ own accounts.⁵⁵⁹ This messaging improperly contributed to physicians’ false sense of security in the belief that prescription opioids can be prescribed without substantial risk. (See Appendix I). Further, misleading statements by Defendants on the efficacy of opioids in the treatment of chronic pain (see Appendix I) are inconsistent with the medical evidence that pain improves in many chronic pain patients who are tapered down and/or off of opioids.

⁵⁵⁶ *Id.* at p. 2118.

⁵⁵⁷ Lester, W., et al. Symptomology Associated with In Utero Exposures to Polysubstance in an Appalachian Population. Marshall Journal Of Medicine. 2019; 5(2):38-51, at pp.38,41.

⁵⁵⁸ Paulozzi LJ, et. al. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiology and Drug Safety. 2006;15:618-627, at p. 621; Appendix III to this report.

⁵⁵⁹ Rieder TN. In opioid withdrawal, with no help in sight. *Health Aff.* 2017;36(1):182-185.
doi:10.1377/HLTHAFF.2016.0347

10. Increased supply of prescription opioids contributed substantially to diversion of prescription opioids to individuals for whom they had not been prescribed (The Tsunami Effect).

- a. As stated in the 2013 CDC Report: “Almost all prescription drugs involved in abuse come from prescriptions originally. However, once they are prescribed and dispensed, prescription drugs are frequently diverted to people using them without prescriptions. There are instances where pharmacies are dispensing large quantities of opioids as part of an illegal distribution scheme as well as pharmacists who fail to meet their obligation to determine that a prescription was issued for a legitimate medical purpose.”⁵⁶⁰
- b. This quote highlights the large role that diversion of prescription opioids has played in the current epidemic. In addition to people getting addicted to and being harmed by opioids prescribed directly to them, millions have been harmed through diversion of prescription opioids to unauthorized sources, from teenagers experimenting to people already addicted to opioids gaining easier access through the illicit market.
- c. An efficient distributor supply chain made prescription opioids available on a mass scale to large numbers of people in rural and remote settings, as well as urban and suburban settings, expanding both the licit and illicit drug market, and setting this opioid epidemic apart from prior epidemics and other drug epidemics. The sheer scale of access to opioids made possible through the distribution and supply chain, led individuals who otherwise would never have been exposed, to use and subsequently be killed or harmed by opioids.⁵⁶¹
- d. It is important to recognize that although many of the communities hit hardest by the opioid epidemic were already struggling with serious social and economic problems, the sudden availability of and easy access to opioids, initially in prescription pill form, contributed to the economic and

⁵⁶⁰ United States Department of Health and Human Services. Addressing Prescription Drug Abuse in the United States. :1-36, at p. 16. *See* https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf.

⁵⁶¹ *See also*, paragraph, above, re likely extent of diversion of prescription opioids.

social devastation of many towns across America.⁵⁶² Economic downturn and the efflux of manufacturing jobs in towns across America in the last thirty years, have contributed to so-called “deaths of despair”—early mortality in middle aged non-Hispanic whites due primarily to drug overdose.⁵⁶³ Nonetheless, economic disadvantage contributes only 10-20% of mortality risk attributable to opioids, whereas the larger share of risk is due to supply of opioids in a given geographic region.⁵⁶⁴

- e. ARCos data on opioid prescribing show a 9% increase in opioid-related hospitalizations for each one morphine kilogram equivalent increase in opioid sales at the county level.⁵⁶⁵ These data demonstrate a clear and convincing geographic-specific link between opioid dispensing and opioid related harm.⁵⁶⁶
- f. Khan *et al.*, writing in *JAMA Internal Medicine* in 2019, show that an opioid prescription to one family member increases the risk of opioid overdose death to others in the same family, even though they do not have an opioid prescription. This study identifies 2,303 individuals who experienced opioid overdose and 9,212 matched control individuals, and shows that any prior opioid dispensing to family members was associated with overdose (odds ratio [OR], 2.89 [95% CI, 2.59-3.23]) in other family members. Risk of overdose increased in a dose-response fashion: Odds of overdose (>0-<50 morphine milligram equivalents per day: OR, 2.71 [95% CI, 2.42-3.03]; 50-<90 morphine milligram equivalents per day: OR, 7.80 [95% CI, 3.63-16.78]; ≥90 morphine milligram equivalents per day: OR, 15.08 [95% CI, 8.66-26.27]).⁵⁶⁷

⁵⁶² Ruhm CJ. Deaths of Despair or Drug Problems? NBER Working Paper No. 24188, NBER Program(s):Health Care, Health Economics, Public Economics, *National Bureau of Economic Research, Inc.* (2017).

⁵⁶³ Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci.* 2015. doi:10.1073/pnas.1518393112, at p. 15081.

⁵⁶⁴ Ruhm, *et al.*, “Deaths of Despair,” fn. 562, above.

⁵⁶⁵ Gherter R. U.S. County Prevalence of Retail Prescription Opioid Sales and Opioid-Related Hospitalizations from 2011 to 2014. *Drug and Alcohol Dependence* 194 (2019) 330–335, at p.330.

⁵⁶⁶ *Id.* at p. 333.

⁵⁶⁷ Khan NF, Bateman BT, *et al.* Association of Opioid Overdose with Opioid Prescription to Family Members. *JAMA Intern Med.* doi:10.1001/jamainternmed.2019.1064, at p. E3.

- g. The recent NASEM report on guidelines for opioid use for acute pain (NASEM 2020), referenced above, further states that “Opioids pose risks not only to the patients for whom they are prescribed, but also to family members and to the community. Unused opioid pills from opioid prescriptions can be diverted to family members and friends (Bicket et al., 2019; Hill et al., 2017; Howard et al., 2019; Thiels et al., 2017). These unused pills, which often are not disposed of properly, may be used by the patient for indications other than those for which they were prescribed (e.g., as a sleep aid), or they may be used by someone other than the patient (Bicket et al., 2017; Jones et al., 2014). Individuals with opioid use disorder commonly report that they started by misusing prescription opioids (Ali et al., 2019; Becker et al., 2008; Cicero et al., 2014; NASEM, 2019). Furthermore, there is an association between the size of a patient’s opioid prescription and the likelihood of an opioid overdose among the patient’s family members (Khan et al., 2019). This association is present in children and adolescents as well as in adults (Khan et al., 2019). Among individuals who misuse prescription opioids, the most common source of opioids was pills from family members and friends. Among individuals who use heroin, the majority (66%) previously misused prescription opioids (Cicero et al., 2014). *Thus, opioid overprescribing, that is, prescribing more opioids than are necessary to control a patient’s acute pain, is a factor contributing to the public health epidemic of opioid overdoses.*⁵⁶⁸
- h. Finally, an objective observer would have appreciated that the number of opioid pills being shipped to pharmacies all over the United States was far in excess of medical need. For example, the Annual Production Quotas (APQs) that were approved by the DEA, despite FDA recommendations for lower amounts, were based on industry claims of market demand, without consideration of legitimate medical need or the likelihood that the APQs reflected substantial diversion.⁵⁶⁹ The DEA routinely accepted sales figures and unsupported claims of increased demands as a proxy for the legitimate needs of the United States.⁵⁷⁰ The West Virginia Attorney

⁵⁶⁸ NASEM 2020, fn. 537, above, at pp. 15-16 (emphasis added).

⁵⁶⁹ West Virginia Attorney General, “DEA’s failure”, fn 55, above , at p. 29

⁵⁷⁰ *Id.*

General's office concluded that APQs "were clearly excessive from 2010-2016."⁵⁷¹

11. The increased supply of prescription opioids through licit and illicit sources resulted in a prescription opioid epidemic in the United States. "Epidemic," defined as an outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990's and continuing to the present day.

- a. The societal effects of this opioid epidemic are worse than the societal effects of other drug epidemics, because of the accelerated devastation to individuals and communities, including high rates of pregnant women being exposed to opioids and giving birth to babies dependent on opioids; who in turn suffer long-term cognitive consequences;⁵⁷² the tragic disruption to families and communities due to loss of parental caregivers,⁵⁷³ requiring substantial resources for foster care; exodus from the work force as a result of opioid dependence and addiction;⁵⁷⁴ and high rates of addiction and death in young people in the prime of their lives.⁵⁷⁵
- b. Long-term effects of Prenatal Opioid Exposure (POE): In a recent *JAMA* meta-analysis, the authors reported statistically significant cognitive and motor deficits among children exposed to prenatal opioids compared to unexposed children, from birth through age 6; deficits found among children from age 7-18 were no longer statistically significant.⁵⁷⁶ The authors stated, "The cause and association of this with POE or other

⁵⁷¹ *Id.*, at p. ES-4.

⁵⁷² Yeoh SJ, *et al.* Cognitive and motor outcomes of children with prenatal opioid exposure: a systemic review and meta-analysis. *JAMA Network Open*. 2019; 2(7): 1-14, at pp. 1-2.

⁵⁷³ Radel L, Baldwin M, *et al.* Substance use, the opioid epidemic, and the child welfare system: key findings from a mixed methods study. *ASPE Research Brief*. (March 7, 2018)

⁵⁷⁴ Franklin GM, *et al.* Early opioid prescription and subsequent disability among workers with back injuries. *Spine*. 2008; 33(2): 199-204; *see also* Anora M. Gaudiano, *How the opioid epidemic is exacerbating a US labor-market shortage*. MarketWatch, June 29, 2018. <https://www.marketwatch.com/story/how-the-opioid-epidemic-is-exacerbating-a-us-labor-market-shortage-2018-06-28>.

⁵⁷⁵ From 2012 to 2015 there were 621 opioid related overdose deaths in those under age 35 in West Virginia, with 135 of those being oxycodone. West Virginia Drug Overdose Deaths Historical Overview 2001-2015, West Virginia Department of Health and Human Resources, August 17, 2017, at p.9, https://dhhr.wv.gov/oeps/disease/ob/documents/opioid/wv-drug-overdoses-2001_2015.pdf.

⁵⁷⁶ Yeoh, "Cognitive and Motor Outcomes", fn. 572, above.

factors (*e.g.*, withdrawal treatment) are uncertain but suggest that POE necessitates long-term support and intervention.”⁵⁷⁷ It should be noted that, to the extent that “withdrawal treatment” may be a cause of the observed deficits, such treatment itself would not have been required if not for the POE that precipitated the withdrawal and accompanying need for treatment. Further, “children with POE are 3 times more likely to have severe intellectual disability according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria Poor neurodevelopmental outcomes in children with POE, even from an early age, is not novel information. However, our data appear to indicate that neurodevelopment did not improve after preschool and worsened by school age.”⁵⁷⁸

- i. Similar results were reported in a study of the academic testing of Australian children who had been diagnosed with NAS at birth. Test scores of NAS children were compared to those of matched controls and the general population, at Grades 3, 5, 7, and 9, which correspond to ages 8-9, 10-11, 12-13, and 14-15, respectively. The authors reported, “Our results show that a diagnosis of NAS is associated with poorer performance in standardized and compulsory curriculum-based tests from as early as 8 or 9 years of age in grade 3 of school when compared with other NSW [New South Wales] children, including those who were matched for gender, gestation, and socioeconomic status. Indeed, by the first year of high school, children with NAS performed even more poorly than other children in grade 5 who were, on average, 2 years younger. By grade 7, 44% of children with NAS had failed to meet NMS [National Minimum Standards] in ≥1 domain of testing.”⁵⁷⁹
- ii. While noting that the cause for these effects is “uncertain,” the authors cited known biological mechanisms that could reasonably explain the deficits: “NAS is caused by transplacental exposure to drugs of addiction or dependency that interfere with brain function

⁵⁷⁷ *Id.* at p. 2.

⁵⁷⁸ *Id.* at pp. 8-9.

⁵⁷⁹ Oei JL, et al. Neonatal Abstinence Syndrome and High School Performance. *Pediatrics*. 2017;139(2):e20162651, at p. 7

and development. Opioids impair adult brain function and cognitive skills even after only a few days of use, and their effects on the developing brain are subtle but long-lasting and include alterations to neuronal apoptosis, dendritic morphogenesis, and neurotransmitter homeostasis.”⁵⁸⁰ Further, the risk of failure to meet NMS (OR=2.5) was greater for NAS than for any other risk factor investigated.⁵⁸¹

- iii. The consistency of results from the Yeoh and Oei studies provides support for the conclusion that NAS contributes substantially to persistent developmental deficits. “This finding is of great concern because school failure increases the risk of myriad poor adult outcomes, including depression in women, criminal activity, and drug use. We showed that children with NAS performed more poorly in all 5 test domains, including reading or literacy skills, 1 of the most important predictors of school success. Children who cannot read at expected levels by grade 3 are less likely to enroll in college or graduate high school. In the United Kingdom, two-thirds of prisoners have a reading age <11 years. Furthermore, test results in children with NAS worsened as they entered high school.”⁵⁸²
 - iv. A recent study found developmental delays among infants exposed to opioids in utero, even where the newborns displayed no overt symptoms of NAS. The authors reported, “Compared to infants with no detected exposures the diagnosis of developmental delay was highest among infants with NAS (7.6% versus 28.3%). However, the diagnosis was still twice as likely among opioid exposed infants without NAS (7.6% versus 15.6%).”⁵⁸³
- c. Loss of Parental Caregivers and Impacts on Foster Care: A 2018 study of the relationship between drug use and foster care reported, “Higher rates of overdose deaths and drug hospitalizations correspond with higher child welfare caseload rates. We estimate that in the average county nationwide,

⁵⁸⁰ *Id.*

⁵⁸¹ *Id.*

⁵⁸² *Id.*

⁵⁸³ Hall ES *et al.* Developmental disorders and medical complications among infants with subclinical intrauterine opioid exposures. *Population Health Management*. 2019;22;19-24, at p. 21.

a 10 percent increase in the overdose death rate corresponded to a 4.4 percent increase in the foster care entry rate. Similarly, a 10 percent increase in the average county's drug-related hospitalization rate corresponded to a 2.9 percent increase in its foster care entry rate.”⁵⁸⁴ While the increased rates of overdose deaths are not exclusively linked to opioids, data cited previously support the significantly greater share of drug mortality attributable to opioids than to other drugs.⁵⁸⁵ The increased need for foster care is supported by the California State data described above, showing the substantial increase in opioid mortality among individuals between ages 25-44, who were in their prime child-rearing years when they died.

- d. Exodus from the workforce: It is well-known that widespread distribution and use of opioids has had a significant adverse effect on the availability of workers, both due to increased mortality and the myriad problems associated with opioid use. According to a recent analysis, “The opioid epidemic is preventing a huge portion of the population that is sidelined from joining the labor force because labor intensive jobs are also the ones that require workers who can pass drug tests.”⁵⁸⁶ The opioid epidemic is responsible for this detrimental impact. Franklin (2008) found that “receipt of opioids for more than 7 days (odds ratio 2.2; 95% confidence interval, 1.5–3.1) and receipt of more than 1 opioid prescription were associated significantly with work disability at 1 year.” Note also that a study of labor force loss due to opioids estimates 919,400 individuals out of work force due to opioids in 2015.⁵⁸⁷
- e. Overdose (“OD”) deaths: A study by Dunn *et al.* found an increased risk of opioid-related overdose death in a step-wise dose response relationship:

⁵⁸⁴ Radel, “Child Welfare System”, fn. 573, above, at p. 2-3.

⁵⁸⁵ See, e.g., Ctrs. for Disease Control and Prevention, *Opioid Overdose*, <https://www.cdc.gov/drugoverdose/index.html>: “Drug overdose deaths continue to increase in the United States. From 1999 to 2017, more than 702,000 people have died from a drug overdose. In 2017, more than 70,000 people died from drug overdoses, making it a leading cause of injury-related death in the United States. Of those deaths, almost 68% involved a prescription or illicit opioid.” (emphasis added).

⁵⁸⁶ Anora M. Gaudiano, *How the Opioid Epidemic Is Exacerbating a US Labor-Market Shortage*, MarketWatch (June 29, 2018), <https://www.marketwatch.com/story/how-the-opioid-epidemic-is-exacerbating-a-us-labor-market-shortage-2018-06-28>.

⁵⁸⁷ Ben Gitis, Isabel Soto, *The Labor Force and Output Consequences of the Opioid Crisis*, American Action Forum (Mar. 27, 2018), <https://www.americanactionforum.org/research/labor-force-output-consequences-opioid-crisis/>.

“Compared with patients receiving 1 to 20 mg/d of opioids (0.2% annual overdose rate), patients receiving 50 to 99 mg/d had a 3.7-fold increase in overdose risk (95% CI, 1.5 to 9.5) and a 0.7% annual overdose rate. Patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk (CI, 4.0 to 19.7) and a 1.8% annual overdose rate. … Patients receiving higher doses of prescribed opioids are at increased risk for overdose, which underscores the need for close supervision of these patients.”⁵⁸⁸ The HRs from the Dunn study are represented in the graph at paragraph 11.b. iii, below.

- i. Dunn reported that 4 of the 51 overdose cases (7.8%) “had notes indicating overdoses associated with applying extra fentanyl patches or sucking on a patch.”⁵⁸⁹ This represents a 13-fold multiple of the small percentage of patients in the study population who used the fentanyl patch (0.6%).⁵⁹⁰ This is consistent with fentanyl’s known lethality (50-100 times as potent as heroin), which may be moderated by the mechanism of a patch on the skin, but is not moderated when multiple patches are used or the patch is chewed to release the full dose at once. Furthermore, if the patch or the individuals’ skin is at a higher temperature, it will release fentanyl more quickly, increasing risk of overdose even when used as indicated.
- ii. In the Dunn study, the authors noted that the risk analysis was based on a comparison of overdose events among higher dose patients to those who received lower doses, rather than the patients who received none.⁵⁹¹ The authors also provided data on the rate of ODs at all levels of exposure, including those with no exposure, and these data further demonstrate the magnitude of increased risk. For the population with no prescribed opioids, the OD rate was 36 per 100,000 person years (PYR), while increasing to 677 per 100,000 PYR at doses of 50-99 mg, and 1791 per 100,000 PYR at doses of 100 mg or greater, representing rate increases of 18.8 and

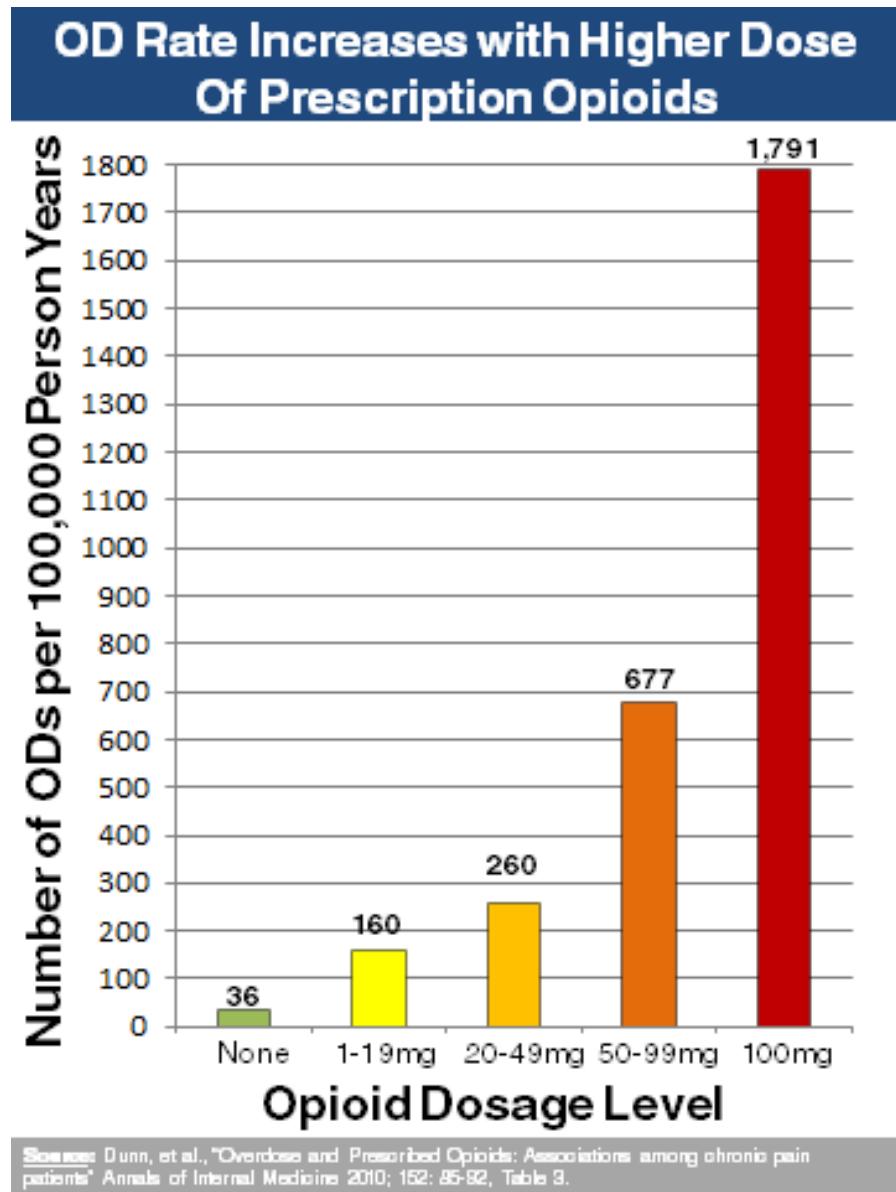
⁵⁸⁸ Dunn KM, Saunders KW, Rutter CM, *et al.* Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann Intern Med.* 2010;152(2):85-92, at p. 85.

⁵⁸⁹ *Id.* at p. 88.

⁵⁹⁰ *Id.* at Table 1, p. 88.

⁵⁹¹ *Id.* at p. 90

49.8, respectively, compared to no prescription opioid use.⁵⁹² These data are represented in the graph below:

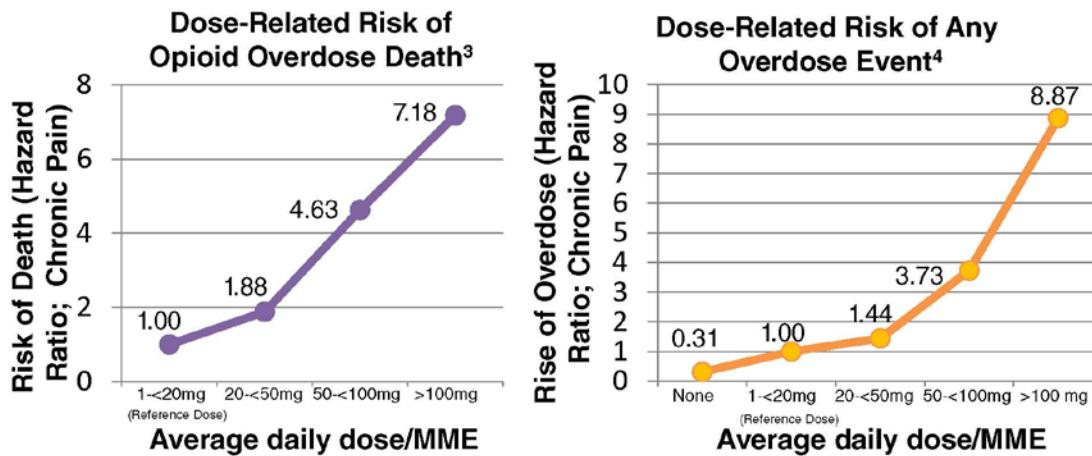


⁵⁹² *Id.* at Table 3, p. 89.

iii. Dunn also noted that their study “provides the first estimates that directly link receipt of medically prescribed opioids to overdose risk, and suggests that overdose risk is elevated in patients receiving medically prescribed opioids, particularly in patients receiving higher doses.”⁵⁹³ These are important data, since they directly refute the Industry’s position that only those who misuse the drugs are at risk of OUD and mortality.

“Higher Dosage, Higher Risk”¹

“Higher dosages of opioids are associated with higher risk of overdose and death—even relatively low dosages (20-50 morphine milligram equivalents (MME) per day) increase risk. Higher dosages haven’t been shown to reduce pain over the long term.”²



1. Centers for Disease Control and Prevention, Calculating Total Daily Dose of Opioids For Safer Dosage, https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf.

2. *Id.*

3. Bohnert AS *et al.* Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths. *JAMA*. 2011;305(13):1315-1321. at p. 1319.

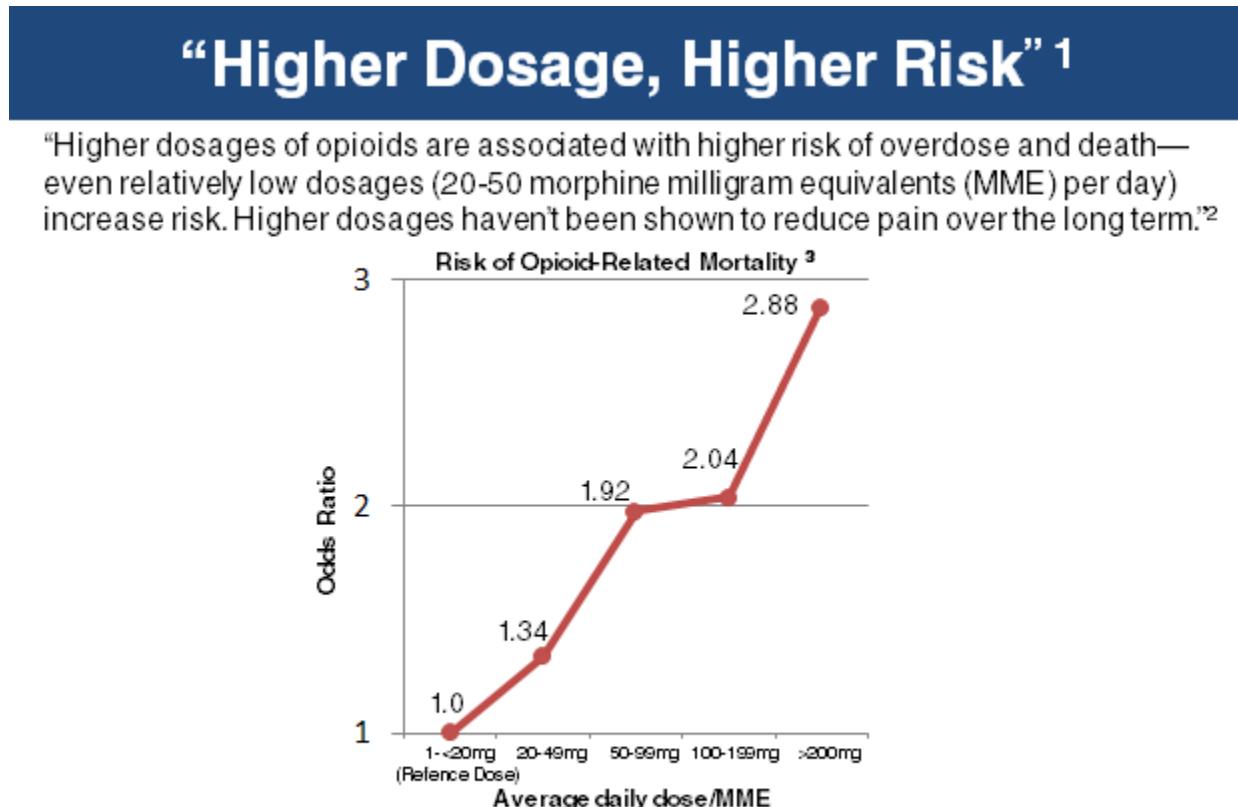
4. Dunn KM *et al.* Opioid Prescriptions for Chronic Pain and Overdose. *Ann Intern Med*. 2010;152:85-92, at p. 89.

⁵⁹³ *Id.* at p. 90.

- iv. As shown in the graph above, studies by Dunn *et al.* and by Bohnert *et al.* both found an increased risk of opioid-related overdose death at each level of increased dose, and particularly at doses greater than 100 MME. In the Dunn study, compared to the reference dose of 1-<20 mg, the adjusted hazard Ratio (HR) for 20-<50 mg was 1.44; for 50-100 mg, the HR was 3.73; and for > 100 mg, the HR was 8.87. In the Bohnert study, Compared to the same reference dose of 1 to < 20 MME, the HR for 20 to < 50 mg was 1.88; for 50 to < 100 mg, the hazard ratio was 4.63; and at > 100 mg, the hazard ratio was 7.18. All results were statistically significant. A similar pattern held for each of three diagnostic groups in the Bohnert study (substance use disorders, chronic pain, and cancer): “The adjusted hazard ratios (HRs) associated with a maximum prescribed dose of 100 mg/d or more, compared with the dose category 1 mg/d to less than 20 mg/d, were as follows: among those with substance use disorders, adjusted HR = 4.54 (95% confidence interval [CI], 2.46-8.37; absolute risk difference approximation [ARDA] = 0.14%); among those with chronic pain, adjusted HR = 7.18 (95% CI, 4.85-10.65; ARDA = 0.25%); among those with acute pain, adjusted HR = 6.64 (95% CI, 3.31-13.31; ARDA = 0.23%); and among those with cancer, adjusted HR = 11.99 (95% CI, 4.42-32.56; ARDA = 0.45%).”⁵⁹⁴ Opioid therapy is generally accepted as appropriate for cancer patients, especially in late stages or severe pain. Nevertheless, with the advent of improved cancer therapies, more patients are living longer with disease or remission, and opioid therapy should be implemented with caution, to minimize risk of addiction.
- v. A population based nested case control study of 607,156 people prescribed opioids found that an average daily dose of 200 mg or more of morphine or equivalent was associated with a nearly 3-fold, statistically significant increased risk of opioid-related mortality relative to low daily doses (< 20 mg of morphine or

⁵⁹⁴ Bohnert, et al., “Association Between Prescribing Patterns,” fn. 508, above, at p.p. 1315; Olsen, *et al.*, “Pain relief that matters”, fn. 264, above.

equivalent), Odds Ratio (OR) 2.88, 95% CI 1.79-4.63.⁵⁹⁵ This is illustrated in the graph below:



¹Centers for Disease Control and Prevention, Calculating Total Daily Dose of Opioids For Safer Dosage, https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf.

²Id.

³Gomes T, et al. Opioid Dose and Drug-Related Mortality in Patients with Nonmalignant Pain. *Arch Intern Med.* 2011;171(7): 686-691, at p. 690

- vi. A 2019 cohort study from the United Kingdom examined 98,140 new long-term (three or more opioid prescriptions within 90 days) opioid users for 3.4 years. The authors found that “[l]ong-term opioid use is associated with serious adverse events such as major

⁵⁹⁵ Gomes *et.al.*, “Opioid Dose,” fn. 554, above, at p. 686. It is noteworthy that Gomes studied “Non-Malignant Pain,” without regard to duration of exposure, requiring only “at least one” opioid prescription in the 120 days prior to death. (p. 687) This may explain the lower relative risk in the Gomes study compared to those in Bohnert (study of pain patients specified those with “chronic pain” conditions) and Dunn (inclusion criteria required 3 or more opioid prescriptions within 90 days prior to the overdose). As Edlund demonstrated, duration of exposure is a key factor in determining the magnitude of increased risk of opioid-related harm.

trauma, addiction and overdose. The risk increases with higher opioid doses.”⁵⁹⁶

- vii. The evidence of increased dose as the cause of higher mortality is supported by evidence of the converse, that is, lower mortality following decreased dose. Recent experience in Oregon demonstrated a significant decrease in overdose deaths after policies were implemented to prioritize non-opioid pain management and to lower the doses when opioid therapy was prescribed.⁵⁹⁷
- viii. We are now in the second and third waves of this epidemic, with a spike in deaths from illicit opioids, particularly heroin (second wave) and illicit fentanyl (third wave). The prescription opioid epidemic led to transition to heroin/fentanyl, and the cumulative death toll remains higher for prescription opioids, despite recent spikes in fentanyl-related mortality.
- ix. Based on CDC data, between 1999 and 2018, 245,218 people died from opioid pain relievers (excluding non-methadone synthetics, predominantly fentanyl). In the same time period, 115,568 died from heroin, and 124,486 people died from non-methadone synthetics (predominantly fentanyl), for a total of 240,054 deaths due to heroin and illicit fentanyl. Although these numbers are staggering, the cumulative death toll from opioid pain relievers through 2018 (245,218) was more than that of heroin and illicit fentanyl combined (240,054).⁵⁹⁸ In short, while there has been an

⁵⁹⁶ Bedson J, Chen Y, Ashworth J, Hayward RA, Dunn KM, Jordan KP. Risk of adverse events in patients prescribed long-term opioids: A cohort study in the UK Clinical Practice Research Datalink. *Eur J Pain*. 2019; 23:908-922, at p. 908.

⁵⁹⁷ Hedberg K, et al. Integrating public health and health care strategies to address the opioid epidemic: the Oregon Health Authority’s opioid initiative. *Journal of Public Health Management & Practice*. 2019;25(2):214-220, at pp. 214-215.

⁵⁹⁸ Centers for Disease Control and Prevention, *Data Brief 356. Drug Overdose Deaths in the United States, 1999–2018*, at Data Table for Figure 3, https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf. Recently released provisional mortality data reported 12,068 prescription-opioid-related deaths in 2019, and 51,415 total deaths related to heroin and fentanyl in that year. These data if confirmed, will cause heroin and fentanyl deaths to exceed those related to prescription opioids for the first time in the 20+ year history of the epidemic. Katz, J., et al., In Shadow of Pandemic, U.S. Drug Overdose Deaths Resurge to Record. The New York Times, July 15, 2020. <https://www.nytimes.com/interactive/2020/07/15/upshot/drug-overdose-deaths.html>.

obvious recent spike in deaths related to heroin and illicit fentanyl, the number of deaths caused by non-fentanyl prescription opioids remains unacceptably high, and cumulatively exceeds deaths associated with heroin and fentanyl.

- x. Prescription opioid related deaths, excluding fentanyl and methadone, continued to rise through 2017, with 2018 registering the first substantial annual decline in prescription opioid related deaths since 1999 (14,495 deaths in 2017; 12,550 in 2018).⁵⁹⁹ A report recently released by the CDC shows that drug overdose deaths in women aged 30–64 years due to prescription opioids have been steadily rising between 1999 and 2017. “The crude rate for deaths involving prescription opioids increased from 1999 to 2017 for every age group, with the largest increases (>1,000%) among women aged 55–64 years.”⁶⁰⁰
- f. Nonfatal overdose: While fatal cases justifiably capture our attention, it must also be recognized that the cost of a nonfatal overdose is far greater in terms of medical and community resources, both in terms of medical costs to treat the overdose episode itself, and to provide long-term care for an OUD that may have given rise to the overdose event.
 - i. According to the CDC, among approximately 45 million emergency department visits reported by the 16 Enhanced State Opioid Overdose Surveillance (ESOOS) states from July 2016 through September 2017, “a total of 119,198 (26.7 per 10,000 visits) were suspected opioid overdoses.”⁶⁰¹
 - ii. Unlike the available fatal overdose data, which are categorized according to non-fentanyl prescription opioids, heroin, etc., the CDC/ESOOS on emergency department visits are not broken out into categories. Although the cumulative total of prescription opioid mortality since 1999 exceeds mortality for fentanyl plus

⁵⁹⁹ *Id.*

⁶⁰⁰ VanHouten JP, Rudd RA, Ballesteros MF, Mack KA. Drug Overdose Deaths Among Women Aged 30–64 Years — United States, 1999–2017. *MMWR Morb Mortal Wkly Rep.* 2019;68(1):1–5, at p. 2.

⁶⁰¹ Vivolo-Kantor AM, Seth P, Gladden RM, et al. Vital Signs: Trends in Emergency Department Visits for Suspected Opioid Overdoses — United States, July 2016–September 2017. *MMWR Morb Mortal Wkly Rep.* 2018;67:279–285, at p. 281.

heroin, the mortality rate for the latter category has recently begun to exceed the former; it is likely that the nonfatal overdose hospital admissions have occurred in a similar ratio of prescription opioids to illicit heroin and fentanyl.

- iii. Tens of thousands of Americans experience non-fatal overdose, both in medical settings, like the emergency department, and in the field, creating a significant burden on the health care system and on first responders, not to mention the victims of near overdose themselves. In the paper by Dunn *et al.*, previously discussed, the authors found “[m]ore than 7 nonfatal overdose events occurred for each fatal overdose” in the study cohort.⁶⁰² “The overall overdose rate in the sample was 148 per 100,000 person-years, indicating that fatal overdose represents only the tip of the iceberg (88% of identified overdose events were nonfatal). Most of the nonfatal overdoses were clinically serious.”⁶⁰³ These data mean that on a nationwide basis, the over 14,000 fatal prescription opioid overdoses in 2017⁶⁰⁴ would translate to over 100,000 nonfatal overdoses during that same year. Similarly, the approximately 1000 opioid-related overdose deaths in Cabell County between 2001-2018 would translate to over 7,000 non-fatal overdoses.
- g. Suicide: The 2019 cohort study from the United Kingdom which examined 98,140 new long-term (three or more opioid prescriptions within 90 days) opioid users for 3.4 years, and found that long-term use was associated with serious adverse events, also found that the risk of suicide by intentional overdose increases with higher opioid doses.”⁶⁰⁵ The authors also report that intentional opioid overdose was nearly 4x more likely in patients prescribed long-term opioids at the highest doses (>50mg)..⁶⁰⁶

⁶⁰² Dunn, *et al.*, “Opioid Prescriptions,” fn. 588, above, at p. 89.

⁶⁰³ *Id.*, p. 91.

⁶⁰⁴ CDC, Data Brief 356, fn. 598, above, at p. 4.

⁶⁰⁵ Bedson J, Chen Y, Ashworth J, Hayward RA, Dunn KM, Jordan KP. Risk of adverse events in patients prescribed long-term opioids: A cohort study in the UK Clinical Practice Research Datalink. *Eur J Pain*. 2019; 23:908-922, at p. 908.

⁶⁰⁶ *Id.* at p. 913.

- i. Writing in the journal *Pain*, Ilgen *et al.* found that the higher the dose of opioids, the greater the suicide risk, an association which was not present in patients with chronic pain on acetaminophen, a non-opioid pain pill. The authors write, “Increased dose of opioids was found to be a marker of increased suicide risk, even when relevant demographic and clinical factors were statistically controlled There was no significant association between acetaminophen dose and regimen and suicide risk, suggesting that the observed effects may be specific to opioids.”⁶⁰⁷
 - ii. In a *New England Journal of Medicine* article on opioids and suicide risk, Bohnert *et al.* note that “A reduction in the quantity of prescribed opioids may function as a ‘means restriction’ by reducing patients’ access to a lethal means of causing an intentional or unintentional opioid overdose. To this end, clinicians should ask about their patients’ access to opioids, including past prescriptions and medications prescribed to others in the same home. Taper protocols that involve small decreases in dosage over time are successful for reducing dosages and may actually reduce pain intensity. However, whether tapering changes the risk of either suicide or overdose is unknown.”⁶⁰⁸
 - iii. As above, intentional opioid overdose, *i.e.* suicide, was nearly 4x more likely in patients prescribed long-term opioids at the highest doses (>50mg).⁶⁰⁹
- h. Opioids are associated with more adverse medical outcomes and increased mortality and morbidity than non-opioid analgesics (NSAIDs),⁶¹⁰ contrary

⁶⁰⁷ Ilgen MA, Bohnert AS, *et al.* Opioid Dose and Risk of Suicide. *Pain*. 2016 May; 157(5): 1079–1084. doi:10.1097/j.pain.0000000000000484, at p. 5.

⁶⁰⁸ Bohnert ASB, Ilgen MA. Understanding Links among Opioid Use, Overdose, and Suicide. *N Engl J Med*. 2019. doi:10.1056/nejmra1802148, at p. 76.

⁶⁰⁹ Bedson *et al.* “Risk of Adverse Events”, fn. 605, above, at p. 913.

⁶¹⁰ Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med*. 2010;170(22):1968-1976. doi:10.1001/archinternmed.2010.391, at p. 1968.

to the claim that morbidity and mortality of non-opioid medications (NSAIDs) for pain are comparable.⁶¹¹

- i. The opioid epidemic is also partly responsible for the spread of Hepatitis C, HIV and other infectious diseases across the country in recent years, as people who become addicted to prescription opioids, transition to injection drug use and share needles with others who are infected. For example, the outbreak of Hepatitis C and HIV in Scott County, Indiana in 2015, “resulted from inappropriate prescribing of opioid medications.”⁶¹²
- j. Misuse and addiction: 11 million people misused prescription opioids in 2016, compared to the approximately 1 million people using heroin. In 2011, according to a CDC report, 11 million people reported nonmedical use of opioid analgesics. “Moreover, chronic nonmedical use of opioid analgesics (*i.e.* nonmedical use on 200 days or more in the past year) increased roughly 75% between 2002-2003 and 2009-2010. This increase means that on average in 2009-2010 there were nearly 1 million people in the U.S. with chronic nonmedical use of opioid analgesics.”⁶¹³ Nearly 2 million (0.8%) of people in the United States are addicted to opioids based on estimates from the 2015 National Survey on Drug use and Health (NSDUH).⁶¹⁴

12. Today’s opioid crisis would not have occurred without the overprescribing and excessive supply of opioids, which together contributed substantially to the scourge of addiction and death.

⁶¹¹ Tayeb BO, Barreiro AE, Bradshaw YS, Chui KKH, Carr DB. Durations of opioid, non-opioid drug, and behavioral clinical trials for chronic pain: Adequate or inadequate? *Pain Med (United States)*. 2016. doi:10.1093/PM/PNW245, at p. 2043.

⁶¹² Strathdee SA, Beyrer C. Threading the Needle — How to Stop the HIV Outbreak in Rural Indiana. *N Engl J Med*. 2015. doi:10.1056/NEJMp1507252, at p. 398.

⁶¹³ United States Dep’t of Health and Human Servs. *Addressing Prescription Drug Abuse in the United States*. 1-36, at pp., 9-10, https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf.

⁶¹⁴ Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Annals of Internal Medicine*. 2017;167(5):293-301. Epub 2017/08/02. doi: 10.7326/m17-0865. PubMed PMID: 28761945, at p. 293.

- a. As I wrote in my book, *Drug Dealer, MD*,⁶¹⁵ doctors were “duped” by the myths that the risk of addiction to prescription opioids was “rare,” and that the drugs were beneficial for chronic pain. I also wrote at that time, and I continue to hold the opinion, that others had some responsibility for the opioid epidemic.
- b. The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services responsible for assuring the safety, effectiveness, and quality of medical drugs. It is responsible for approving drugs before they reach the market, and monitoring the safety and marketing of those drugs after they are publicly available. In my book, *Drug Dealer, MD*, I assigned some responsibility for the prescription drug epidemic to the FDA, and to the Defendants for efforts to influence the FDA.⁶¹⁶
- c. The Toyota-ization of Medicine
 - i. The majority of doctors today work in large integrated health care systems. During the 1990’s and 2000’s, there occurred a mass migration of doctors out of private practice and into managed care organizations. In 2002, 70% of U.S. physician practices were physician-owned. By 2008, more than 50% of U.S. physician practices were owned and operated by hospitals or integrated health delivery systems, and that number continues to rise.⁶¹⁷
 - ii. The migration of doctors into integrated health care systems (hospital factories) has transformed medical treatment. Doctors work much less autonomously. Treatment options are often dictated by hospital administrators, guidelines (*see* Joint Commission, §4.h, above), and third-party payers (health insurance companies). The result is that doctors experience enormous pressure to get patients in and out quickly, to palliate pain, and to

⁶¹⁵ Lembke, “*Drug Dealer, MD*,” fn. 2, above.

⁶¹⁶ Lembke, “*Drug Dealer, MD*,” fn. 2, above; Fauber J. FDA and Pharma: Emails Raise Pay-for-Play Concerns. *Sentinel/MedPage Today*. October 7, 2003, *see* <http://www.medpagetoday.com/PainManagement/PainManagement/42103>, at p. 1.

⁶¹⁷ Kocher R, Sahni N. Hospitals ‘ Race to Employ Physicians — The Logic Behind a Money Losing Proposition. *N Engl J Med*. 2011;1790-1793, at p. 1791.

- have “satisfied customers.” This too has contributed to the problem of overprescribing.⁶¹⁸
- iii. These structural factors opened the doors, but the aggressive misrepresentation of risks and benefits took advantage of these conditions to maximize sales and maximize harm.
 - d. I have also written, in *Drug Dealer, MD*, about the manipulative behaviors of patients in attempting to obtain opioid drugs from their doctors. These behaviors are not surprising; in fact they are diagnostic of the disease of addiction, whether the drug is OxyContin, or Opana, or heroin. In my opinion, the Pharmaceutical Opioid Industry has attempted to blame victims of the disease of addiction for the epidemic resulting from their own misleading statements regarding their dangerously addictive drugs, while at the same time promoting the false message that patients taking these drugs for pain under a doctor’s prescription have little or no risk of addiction or overdose.
 - e. An article published in *Science* in 2018 by Jalal, *et al.*, “Changing Dynamics of the Drug Overdose Epidemic in the United States from 1979-2016,”⁶¹⁹ suggests that mortality data from numerous “drug-specific subepidemics” can be fitted to a smooth exponential curve during that time period. However, the authors note the “paradox” presented by these results, since the data combine mortality associated with subepidemics as disparate as heroin and fentanyl deaths in the northeastern United States with methamphetamines in the southwestern states.⁶²⁰ Accordingly, an after-the-fact fitting of 38 years of combined data to a smooth curve does not obviate the need to understand each subepidemic on its own terms. In the case of prescription opioids, factors relevant to that epidemic have been addressed throughout this report, and are summarized as follows:
- i. The apparent continuity of the overdose mortality rate curve in the Jalal *et al.* article, on closer inspection, shows a definitive rise

⁶¹⁸ Lembke A. Why Doctors Prescribe Opioids to Known Opioid Abusers. *N Engl J Med.* 2012;367(17):1580-1581.

⁶¹⁹ Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science.* 2018. doi:10.1126/science.aau1184.

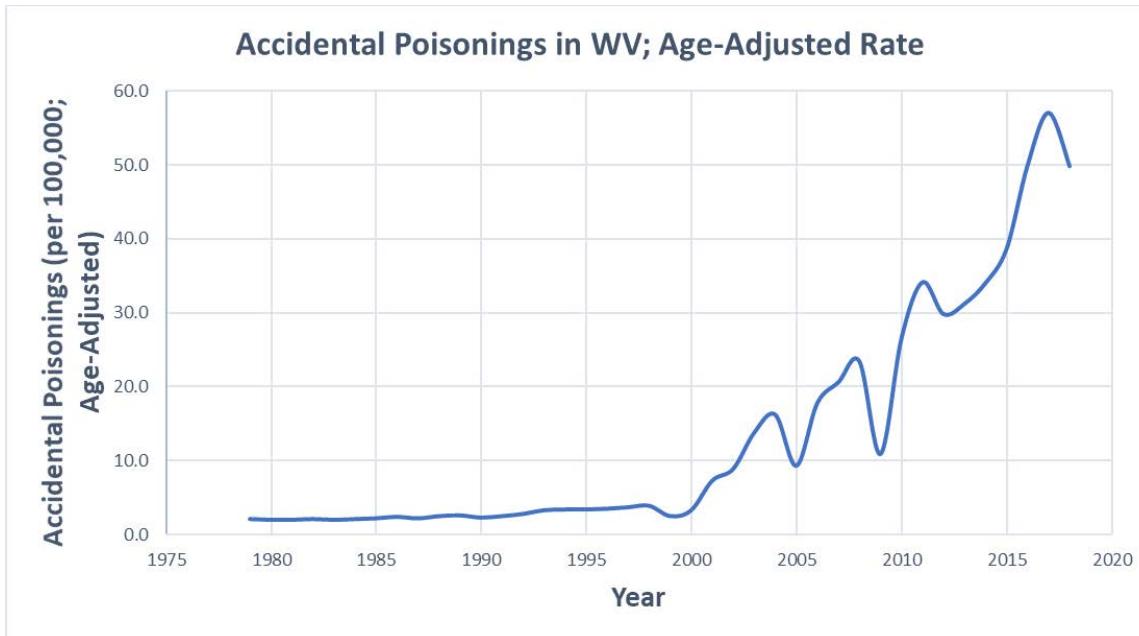
⁶²⁰ *Id.* at p. 1.

above the smooth curve between 2001 and 2010, corresponding to the prescription opioid epidemic.⁶²¹

- ii. The problem of addiction more broadly in society and culture today does not negate the significant role of opioids manufacturers and distributors in causing this epidemic. The misrepresentations of risks and benefits and the oversupply of prescription opioids through the distribution chain were essential contributing factors to the resulting epidemic.
 - iii. Although forces may be operative to accelerate demand, such as despair, loss of purpose, and dissolution of communities, studies show that the ‘push’ of increased access to opioids has played a bigger role than the ‘pull’ of despair.⁶²²
- f. Overdose deaths in West Virginia were low and stable from 1979 until the onset of the prescription opioid epidemic. It has been suggested that there has been an increasing rate of drug overdose deaths from 1979-2016, as part of a unitary drug epidemic in the United States. This argument is flawed, for reasons discussed above. In West Virginia, the data show a convincing pattern of low, and stable, overdose deaths from 1979 until 1999, followed by rapidly increasing overdose mortality in conjunction with the onset of the prescription opioid epidemic, as shown below, based on the report of Gordon Smith, MD, citing official data from the National Center for Health Statistics:

⁶²¹ *Id.*

⁶²² Ruhm, *et al.*, “Deaths of Despair,” fn. 562, above.



13. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.

- a. Primary prevention: Preventing new cases of the disease by limiting access to opioids, re-educating prescribers, and rebuilding communities devastated by the epidemic.
 - i. Opioids should not be prescribed as first line treatment for most forms of pain. Exceptions include cases of severe tissue injury, peri-operatively when multimodal analgesia is insufficient, and as palliative/end of life care.
- A. For acute pain, the CDC guidelines recommend no more than 3 to 7 days of opioid treatment. Even within this general guideline, it is important to limit both the dose and frequency of administration of opioid drugs during the 3-7

day window, to minimize the increase in long-term use that has been documented following higher doses of opioids for acute pain, and to limit the diversion of unused pills.

- B. First line treatment for pain should include non-opioid medications and non-medication treatment for pain (non-opioid medications, physical therapy, psychotherapy). The latter are especially important for the treatment of chronic pain.⁶²³
 - C. There may be unusual instances when opioid medications can be used to good effect in the treatment of chronic pain; but even in this setting, avoiding daily use to avoid tolerance and dependence is recommended. Further, very close monitoring for the emergence of adverse medical consequences, including misuse and addiction, using objective criteria such as urine toxicology and database scrutiny, are essential components of a safe and effective treatment plan. Further, an exit strategy for cessation of opioid therapy is necessary, should risks outweigh benefits at any point in the treatment, in recognition that most patients will have become dependent and will taper with difficulty.⁶²⁴
- ii. Data on the impact of interventions to curb opioid prescribing have recently become available supporting the view that limiting opioid prescribing in a systematic way reduces prescription opioid-related overdose deaths without adversely compromising pain treatment.
- A. Massachusetts had the first of its kind state-wide acute care prescribing limits and a required-check of the Prescription Drug Monitoring Programs (PDMPs) prior to opioid prescribing. As a result it reduced opioid prescriptions by 30%.⁶²⁵

⁶²³ Delgado, *et al.*, “National Variation,” fn. 505, above, at p. 389.

⁶²⁴ Dunn, *et al.*, “Opioid Prescriptions,” fn. 588, above, at p. 86.

⁶²⁵ Sandoe, E., *et al.*, “Policy Levers That States Can Use to Improve Opioid Addiction Treatment And Address the Opioid Epidemic”, Health Affairs Blog. (Oct. 2, 2018).

<https://www.healthaffairs.org/do/10.1377/hblog20180927.51221/full/>

- B. The Department of Public Health determines mean and median quantity and volume of prescriptions for opioids, within categories of similar specialty or practice types. Prescribers who exceed mean or median will be sent notice.⁶²⁶
- C. The law establishes a drug stewardship program to be paid for by drug companies that makes it easier for patients to safely dispose of unwanted and unused medications. Effective Jan. 1, 2017. ⁶²⁷
- D. The State of Massachusetts has launched core competencies for safe prescribing of opioids in the state's medical schools, community health centers, nursing, physician assistant, dental schools and schools of social work." (emphasis in original) Commensurate with decreases in opioid prescribing, Massachusetts has seen a decrease in opioid-related overdose deaths: "Opioid-related overdose deaths in Massachusetts have fallen steadily over the past three quarters even as the presence of fentanyl in overdose deaths reached an all-time high...Overall in 2017 there was a 4 percent decrease in opioid-related overdose deaths from 2016. The data also shows that the Commonwealth has experienced a 30 percent decline in opioid prescriptions since the launch of the Massachusetts Prescription Monitoring Program (MassPAT) in August 2016. ⁶²⁸
- E. A successful program in Chittenden County, Vermont achieved a 50% decline in opioid mortality through a multi-faceted program that included an increased capacity "hub" (the County) and increased number of physicians treating opioid addiction (the "spokes"); a Safe Recovery syringe exchange center and low-barrier sites for buprenorphine treatment; and support for a recent statute requiring such

⁶²⁶ *Id.*⁶²⁷ *Id.*⁶²⁸ *Id.*

medications to be provided to prisoners with addiction treatment.⁶²⁹

- iii. As noted previously, an article in the *New England Journal of Medicine* in 2010 included the comment that prescription opioids are “essentially legal heroin” as well as a comment as to how the FDA should revise a Risk Evaluation and Management Strategy (REMS) for use of opioids, a FDA Advisory Board member stated, “We need to think about how we would construct a REMS if we were going to be marketing heroin.”⁶³⁰ I agree with these statements, since prescription opioids are as addictive as heroin and operate on the same neuro-circuitry in the same manner. Current REMS training is insufficient to educate prescribers about the risks of opioids. We need more comprehensive prescriber training on the evidence of benefits and harms with opioids for medical use, how to monitor patients taking opioids for medical use, how to taper patients off opioids, and how to intervene when a problem arises.
- iv. Medical and nursing schools across the country are beginning to implement addiction medicine curricula, an essential part of the reform process to combat this epidemic. I have led an initiative here at Stanford University School of Medicine to create our first ever addiction medicine curriculum since 2017, and I am involved in promoting similar initiatives across the country.
 - A. As explained at paragraph 26, above, I have been asked to “re-educate” doctors in many jurisdictions, to correct misinformation and provide accurate data on the significant risks and minimal benefits of opioid therapy, particularly for chronic pain. Such re-education is designed to reduce or eliminate over-prescribing of opioids, and thereby reduce or eliminate the panoply of ill effects that they cause

⁶²⁹ City of Burlington, Mayor’s Office, Press Release, “Mayor Miro Weinberger and Community Partners Announce 50 Percent Decline in Opioid-Related Overdose Fatalities in Chittenden County in 2018 (Feb. 14, 2019), <https://www.burlingtonvt.gov/Press/mayor-miro-weinberger-and-community-partners-announce-50-percent-decline-in-opioid-related>.

⁶³⁰ Okie, “A flood of opioids”, fn. 289, above, at p. 1981.

- B. I testified at a White House symposium⁶³¹ on the importance of educating health care providers on addiction treatment and safe prescribing. At that symposium, I suggested a school loan repayment program to incentivize health care providers to treat addiction in underserved areas after completing their training. This suggestion was taken up by Representative Clark and Representative Rogers as the Substance Use Disorder Workforce Loan Repayment Bill, which was included as a key provision in the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act, also known as the SUPPORT Act, passed September 28, 2018. Although the legislation was approved, there is yet to be a source of funding.
- C. I am the Program Director for Stanford’s Addiction Medicine Fellowship, a one-year fellowship to provide advanced training in addiction medicine. I also work on a national level to promote these fellowships, and was the inaugural president of the Addiction Medicine Fellowship Directors’ Association (AMFDA).
- D. I have authored articles on the importance of teaching addiction medicine to medical students, residents, and fellows, including “The Opioid Epidemic as a Watershed Moment for Physician Training in Addiction Medicine” (Academic Psychiatry, 2018)⁶³² and “Qualitative Assessment of Clerkship Students’ Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum (Academic Psychiatry 2018).⁶³³ In these articles, I address the need for more robust training in the screening and intervention of patients with the full spectrum of opioid use disorders (including misuse and

⁶³¹ The Addiction Medicine Foundation, “Congressional Briefing – Addiction Medicine: The Urgent Need for Trained Physicians” (Sep. 28, 2017), <https://www.youtube.com/watch?v=y6kBoQckmHw>.

⁶³² Lembke A, Humphreys K. The Opioid Epidemic as a Watershed Moment for Physician Training in Addiction Medicine. *Acad Psychiatry*. 2018;42(2):269-272. doi:10.1007/s40596-018-0892-8.

⁶³³ Raber I, Ball A, Papac J, Lembke A, et al. Qualitative Assessment of Clerkship Students’ Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum. *Acad Psychiatry*. 2018;42(5):664-667.

- dependence). I further recommend increasing medical school hours of training in addiction medicine, including safe prescribing of controlled substances.
- v. Consider prohibiting the pharmaceutical industry from funding or influencing Continuing Medical Education (CME) courses for prescribers.
 - vi. Consider promoting CME education which explicitly eschews industry funds and influence, and providing academic detailing (unbiased, evidence based information for prescribers).
 - vii. Earmark money to provide medical school, residency, and fellowship training in addiction treatment.
- b. Secondary prevention: limit progression of harm by helping patients on dangerously high doses come down or off of opioids, independent of whether they are addicted, and by implementing harm reduction strategies to mitigate the dangers of opioids.
- i. To accomplish effective, safe, and compassionate opioid tapers in this country, we need funding to build de-prescribing clinics to provide treatment for opioid dependent patients. Where de-prescribing clinics are not feasible, we need to embed an interdisciplinary, chronic care treatment team inside of primary care to support deprescribing/opioid tapering. This chronic care team would consist of physicians, nurses, social workers, case workers, psychologists, and others trained to help patients manage the physically and emotionally taxing process of decreasing prescribed opioids. Primary care doctors, already overloaded with responsibilities, are unlikely to achieve successful tapers in opioid dependent, high dose legacy patients, without significant incentives and support. This will require an enormous investment of resources, as it is estimated that millions of Americans are dependent on opioids and suffering from or at heightened risk for adverse consequences.
 - ii. I worked with colleagues at Stanford to develop a protocol for helping opioid dependent patients compassionately and safely taper down or off of prescribed opioids: “The BRAVO Protocol.” The protocol has been adopted by the Oregon Pain Guidance, the

Oregon Pain Task Force, and has influenced other opioid task forces around the country who are struggling with the problem of opioid dependent (but not addicted) chronic pain patients.⁶³⁴

- iii. We have created a free online continuing medical education course - “The BRAVO Protocol: How to Taper Patients Off of Chronic Opioid Therapy.” This course, created in conjunction with the Stanford continuing medical education office, teaches prescribers how to safely and compassionately taper opioids, something that is not currently taught in medical schools.
- iv. As mentioned above (§A¶24A), our tapering protocol was endorsed by the United States Department of Health and Human Services in 2019, and it became the subject of a Continuing Medical Education course in 2020. The course has also been positively featured in the lay press, highlighting that it features the first-person account of a patient who was, with support, able to taper off of opioids and experienced improved chronic pain as a result.⁶³⁵ We have created a companion page summarizing The BRAVO Protocol, which has gained wide informal distribution among prescribers. It summarizes the key learning points as below. (See BRAVO Protocol summary attached to this report.) The bottom line is, helping patients to decrease or discontinue long term opioid therapy presents a challenging clinical scenario, especially in patients on high doses (greater than 80 MEDs), with moderate to severe chronic pain, and co-occurring mental health disorders (depression, anxiety, PTSD). For this type of complex chronic pain patient, the usual recommendation to decrease opioids by 10% of the starting dose every week frequently will not apply. These patients often need slower tapers on the order of 5-10% decreases or less every month. Expert consensus suggests the taper speed should be tailored to the individual needs of the patient. Some patients who have been on opioids for years to decades, may require *years* to taper their dose. With this complex chronic pain

⁶³⁴ Oregon Health Authority Oregon Opioid Taper Guidelines Task Force Resources. <https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/SUBSTANCEUSE/OPIOIDS/Documents/taskforce/tapering-taskforce/2019-Opioid-Taper-Task-Force-Resources.pdf>.

⁶³⁵ Parloff R. Tapering off long-term Rx opioids: a first-hand account, Opioid Institute. (Oct. 15, 2018), <https://opioidinstitute.org/2018/10/15/tapering-opioids-lembke/>.

patient in mind, the BRAVO protocol outlines a safe and compassionate strategy to approach opioid tapering, while also maintaining a therapeutic alliance between the treatment team and each patient.

- v. Other harm reduction strategies include increasing naloxone distribution, promoting clean needle exchanges, improving patient education regarding safe medication storage and appropriate disposal of excess medications, and increasing public awareness of poison center services. In July 2020, the FDA changed its labeling for opioid pain medication and medication to treat opioid use disorder, to include the statement: "... as a routine part of prescribing these medicines, health care professionals should discuss the availability of naloxone with patients and caregivers, both when beginning and renewing treatment."⁶³⁶

c. Treatment

- i. We need a robust infrastructure to treat addiction, both within and outside the traditional sources for medical care. Such an infrastructure does not currently exist. Instead what we have are siloes of care with limited and contingent funding, or treatment centers accessible only by the rich.
- ii. Addiction treatment should be offered within every hospital, clinic, emergency room, jail, drug court, etc., across America. "Meeting patients where they are" has become a mantra for the field. Patients with this complex behavioral illness are more likely to engage in treatment when they are offered treatment in settings where they are frequently found, like in hospitals, emergency rooms, jails, and even in settings where they might be using drugs (such as at the site of first responders, clean needle exchange sites, safe consumption sites, etc.).
- iii. An effective addiction treatment infrastructure should be based on evidence-based treatments for addiction, including buprenorphine,

⁶³⁶ FDA News Release: FDA Requiring Labeling Changes for Opioid Pain Medicines, Opioid Use Disorder Medicines Regarding Naloxone, July 23, 2020, <https://www.fda.gov/news-events/press-announcements/fda-requiring-labeling-changes-opioid-pain-medicines-opioid-use-disorder-medicines-regarding>

methadone maintenance, and naltrexone. Opioid agonist therapy (buprenorphine or methadone maintenance) has one of the most robust evidence bases of any addiction treatment. Multiple placebo controlled trials over many decades have demonstrated the efficacy of opioid agonist therapy in the treatment of opioid use disorder.⁶³⁷

- iv. Addiction is a chronic relapsing and remitting disorder, requiring a chronic care model and a team based approach, including a peer recovery coach, care coordinator, behavioral health specialist, licensed counselor, and a primary care professional.⁶³⁸ One way to address this problem within our current health care system, is to co-locate behavioral health specialists within primary care, or create a hub and spoke model with specialty clinics providing support to primary care clinics. A concurrent strategy is to build Centers of Excellence for Addiction Treatment at every major medical center around the country, similar to existing Centers of Excellence for cancer, cardiac disease, and diabetes.
- v. As a chronic illness, addiction can require lifelong treatment. In my clinical experience, most people with moderate to severe opioid use disorder struggle to some degree to remain abstinent for the rest of their lives and there is a high rate of relapse when individuals go off of MAT (Medication-Assisted Treatment). Thus, the abatement plan to address the opioid epidemic should focus on providing the maximum level of both MAT and non-MAT resources possible, as quickly as possible, and should maintain this level of treatment long-term, as contemplated in the proposed abatement plan.
- vi. A successful treatment system would allow for those with the disease to titrate their treatment based on illness severity over time, with the recognition that the normal course of addiction involves periods of remission and recurrence, just like cancer.

⁶³⁷ Strang J, Babor T, Caulkins J, Fischer B, Foxcroft D, Humphreys K. Drug policy and the public good: evidence for effective interventions. *Lancet*. 2012;379(9810):71-83, at p. 78.

⁶³⁸ “The Addiction Recovery Medical Home As An Alternative Payment Model,” Health Affairs Blog, December 12, 2018. DOI: 10.1377/hblog20181211.111071. *Heal Aff Blog*. doi: 10.1377/hblog20181211.111071, at p. 3.

- vii. Addiction treatment and recovery requires intensive individual and/or group therapy interventions, which should be integrated into treatment alongside medications.
- viii. Mutual help groups such as Narcotics Anonymous have a long tradition of aiding people with addiction achieve and maintain recovery. New models employing peer counselors as part of an interdisciplinary medical team to treat and target addiction, are being investigated. These models should be considered as a way to bridge inpatient and outpatient treatment and sustain recovery as patients return to their normal lives. Undergirding the creation of a robust infrastructure to target and treat addiction, is the need for a trained workforce to deliver this care.

D. Conclusion

Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. One of the biggest risk factors for addiction is simple access to addictive drugs. When supply of an addictive drug is increased, more people become addicted to and suffer the harms of that drug. The Defendants' conduct in promoting increased supply and widespread access to prescription opioids, including through misleading messaging, has resulted in an epidemic of opioid addiction and overdose death. Increased supply contributed to more pain patients becoming addicted to opioids, including those who turned from prescription opioids to illicit sources of opioids such as heroin (The Gateway Effect). Increased supply contributed to more pain patients and newborns becoming dependent on opioids, increasing their risk for opioid-related morbidity and mortality (The Dependence Effect). Increased supply contributed to more diversion of prescription opioids, causing a dramatic increase in the widespread availability of opioids to persons for whom they had not been prescribed (The Tsunami Effect). The increased supply of prescription opioids through licit and illicit sources resulted in a prescription opioid epidemic in the United States. Others bear some lesser responsibility for the opioid epidemic. However, today's opioid crisis would not have occurred without the paradigm shift encouraged by the Pharmaceutical Opioid Industry, whose actions resulted in the overprescribing and excessive distribution of prescription opioids. In a *New England Journal of Medicine* commentary regarding the CDC Opioid-Prescribing Guideline, CDC physicians Thomas Frieden and Debra Houry stated, "We know of no other medication routinely used for a nonfatal condition that kills patients so frequently."⁶³⁹

⁶³⁹ Frieden TR, Houry D. Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline. *N Engl J Med.* 2016. doi:10.1056/nejmp1515917, at p. 1503.

Lembke Report

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Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted and will accomplish the following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment).

Lembke Report

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Exhibits to this Report:

Attached as Exhibit A is a copy of my current curriculum vitae and a list of all publications authored by me in the past 10 years.

Attached as Exhibit B is a list of data or other information considered by me in forming the opinions expressed herein.

Attached as Exhibit C is a statement of my compensation for services performed in this case.

Attached as Exhibit D is a list of all cases in which I have testified as an expert at trial or by deposition during the past four years.

Pursuant to 28 U.S.C. S 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed on: August 1, 2020



Anna Lembke, M.D.

Anna Lembke, M.D. Report

APPENDIX I

Misleading Promotional Messages

I.A: Purdue Pharma

I.B: Teva/Cephalon

I.C: Janssen

I.D: Endo

I.E: Allergan

Appendix I.A: Purdue Pharma**Purdue Misleading Messaging****A. Benefits of Opioids Overstated****1. *Myth: Opioids are effective for chronic pain***

- "[W]e now know that many patients with chronic, nonmalignant pain respond very well to opioids and that, contrary to our teaching, addiction is very rare and possibly nonexistent as a result of treating such patients with opioids. The barriers to vastly improved treatment for hundreds of thousands of people in pain, are simply the misinformation and prejudice of doctors, pharmacists and regulatory bodies." Purdue Physicians' Pain Management Speaker Training Program, April 18-20, 1997. PKY181654940 at 4966.

Comment: This quote summarizes the essential message promoted initially by Purdue and subsequently by other opioid sellers: that opioids are effective for chronic pain, and that "addiction is very rare and possibly nonexistent," as a result of such treatment. With some variation, the promotional messages detailed in this appendix follow those two themes. As to the claim of efficacy for chronic pain, there was not then, and there has never been, reliable evidence to support the claim; as to the assertion of "rare" addiction risk with opioid therapy, there were numerous studies that had reported a range of addiction as high as 24% before the opioid sellers began the aggressive marketing campaign that omitted any reference to those data, and numerous additional, subsequent studies consistent with the earlier results.

- "Opioid analgesics are indicated for moderate to severe pain that cannot be relieved with other agents. Opioids are effective, easily titrated, and have a favorable benefit-to-risk ratio. Large doses of opioids may be needed to control pain if it is severe, and extended courses may be necessary if the pain is chronic. Tolerance and physical dependence are normal physiologic consequences of extended opioid therapy and must not be confused with addiction. Patients and family members must be educated regarding the difference between tolerance, physical dependence, and addiction. Patients with chronic, severe pain must not consider themselves addicts because they are being treated with opioids. Concerns about addiction should not prevent the appropriate use of opioids. McPhee JS, Schroeder SA. In Lange's Current Medical Diagnosis Treatment, 1996 p 13."

Purdue Physicians' Pain Management Speaker Training Program, April 18-20, 1997. PKY181654940 at 4969.

Comment: This quote builds on the basic message (above) by recommending titration to “large doses,” without disclosing that risk goes up as dose goes up; and by downplaying the significance of physical dependence, which is a significant medical problem.

- Presentation by Dr. Melvin Gitlin entitled “The Use Of Opioids in the Treatment of Chronic Non-Cancer Pain” at the Purdue Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5155-5157 in which he states, “Historically the use of opioids for pain management has been influenced less by scientific data than by subjective attitudes, personal opinion and legislative regulatory influence....Regulatory agencies in the United States are increasingly acknowledging this; some are seeking to reassure clinicians that the legitimate use of opioids should not engender fear of reprisal.... A well designed, double-blind, randomized cross over trial utilizing patient controlled analgesia morphine studied opioid responsiveness in chronic pain. The authors demonstrated that although nociceptive pains exhibited a better analgesic response than did neuropathic pain, approximately 50% of patients with neuropathic pain did show a good or better analgesic response to the opioid.” The study to which Dr. Gitlin refers, by Jadad, et al, “Morphine responsiveness of chronic pain”, Lancet 1992, is not in fact a study of the use of long term opioid therapy in the treatment of chronic pain. Rather it is a study of one-day dosing of opioids in a population of patients with chronic pain, answering an entirely different question than whether opioids work for the treatment of chronic pain. Treating chronic pain patients for a day is not comparable to treating the same population with opioids on a long-term basis.
- Presentation by Dr. Mary Stegman entitled “Pain Management in the Elderly Patient, Special Considerations,” for Purdue's Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5168, in which she states “opioid analgesic drugs are effective for moderate to severe pain,” under the heading “AGS Clinical Practice Guidelines for Chronic Pain,” without clarifying the lack of reliable evidence for the use of opioids in the treatment of chronic pain.

2. *Myth: Opioids are first-line treatment for all types of pain*

- "Opioids are our strongest and safest medications for most disablingly-severe pain. Our obligation is to consider them in all such cases." "Control of Pain: Every Person's Right " Pain Management Speaker Training Program for Physicians, May 5-7, 2000. PKY180170528 at 0545. Part of a Purdue sponsored speakers training program in Beverly Hills, CA.
- "Opioids for Neuropathic Pain--All patients & all types of pain are opioid responsive. There can be variation in the degree of response. May need to titrate to adequate analgesia but intolerable side effects; change opioids. Nociceptive (visceral, somatic) and neuropathic pain responsive to opioids." HSS Training Presentation, August 25, 2000. PKY180435433 at 5565. Purdue sales reps are called "Health Systems Specialists" (HSS) and this was a Purdue Training Presentation for Reps and District Managers.

Comment: The quotes above do not distinguish between acute pain and chronic pain. While there was reliable evidence of efficacy of opioids for acute pain, as noted above and in the Report, there was no reliable evidence of efficacy for chronic, non-cancer pain. It was misleading to make a blanket statement of efficacy without making this distinction clear.

3. *Myth: Opioids are safer than the alternatives*

- "We now know that in appropriately selected patients, opioids have a low morbidity (perhaps less than NSAIDS), and a low addiction potential. Although tolerance may occur in some cases, generally patients become tolerant to bothersome side effects more so than to analgesic effects. Evidence from cancer studies suggests that when patients clinically stable on a certain opioid dose, request a dose escalation, it may be more related to progression in their disease than to tolerance." Physicians' Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057 at 5092.
- Presentation by Dr. Mary Stegman entitled "Pain Management in the Elderly Patient, Special Considerations," for Purdue's Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5166, in which she highlights the risks of acetaminophen, including renal and hepatotoxicity, and in which she claims opioids are "safer than NSAIDS," but never discusses the absolute or relative risks of opioids.

Comment: There was no reliable evidence to claim that opioids were “safer, or “perhaps” safer than NSAIDs or acetaminophen. As to NSAIDs, the best available evidence shows that opioids confer greater risk of mortality and adverse events. (Solomon study); also, the Krebs study (SPACE trial) found more adverse events in the opioid group than among the non-opioid group that consisted of acetaminophen and NSAIDs, with a small percentage of patients on tramadol.

4. *Myth: Opioids improve function and quality of life*

- "In studies of patients with non-malignant pain...Rapid reduction in pain intensity over the first 24 hours; By day three, patients had achieved 94% of their total pain reduction; Patients reported improved ability to sleep, walk, perform normal work, get along with other people, enjoy life." OxyContin Launch Plan, September 27, 1995. PURCHI-003286781 at 6804.
- "Provides quality of life benefits-relative to placebo, OxyContin significantly decreased pain, and improved quality of life, mood and sleep." OxyContin Advertising and Black Box Warnings, June 15, 1998. PKY180625450 at 5455
- "Controlled-release opioids - Cognitive Effects: decreases anxiety, decreased hostility, no declines in cognitive function, improved psychomotor speed, improved sustained attention." Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5175.
- "Benefits of Long acting opioids -- Better pain reduction with better function. Improved sleep. Reduced anxiety. Reduced hostility. No impairment of cognitive function. Improved psychomotor speed. Improved sustained attention." HSS Training Presentation, August 25, 2000. PKY180435433 at 5635.

Comment: The statements above are misleading because they were intended to justify long-term OxyContin therapy for chronic pain, based on short-term studies.

5. *Myth: Not using opioids is tantamount to undertreating pain, is hence immoral, and may make pain worse in the long run.*

- Presentation by Dr. Neil Irick entitled “Can We Justify Undertreating Pain?” for Purdue’s Physician’s Pain Management Speakers Training Program, November 5-7, 1999 in which he invokes The Joint Commission Requirements as justification

and persuasion: "The patient's right to pain management is respected and supported," "Pain as the 5th vital sign," "Statement of patient rights available to all." Dr. Irick also states, "Remember: resolve that no patient should suffer needlessly, listen to the patient, believe the patient, document, be your patient's advocate." PKY181655140 at 5150,5152.

- Presentation by Dr. Mary Stegman entitled "Pain Management in the Elderly Patient, Special Considerations," for Purdue's Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5161 in which she states, "In 2000, JACHO will demand pain TX [treatment]."
- "Based on new literature on the Pathophysiology of pain, it is important to PREVENT the pain as opposed to simply treating the pain. Otherwise, you could have patients develop what is referred to as 'Wind up' which can lead to a complex pain syndrome. Let's say you had a patient present with low back pain from lifting heavy boxes. When that patient lifted the boxes and the injury occurred, the C fibers in his body were stimulated and started firing pulses basically like a strobe light. Those fibers synapsed with the secondary neurons and carried the pain signals to the brain. Think of the secondary neurons like the aperture of a camera, except that instead of the aperture closing when that strobe light hits it, the aperture actually opens. The more light/or stimulus that spills through the aperture, the greater the sensation of pain. So, what happens is even though that stimulus may be diminishing, the threshold for pain has been lowered, and the number of signals have actually increased. This whole process starts a CASCADE OF EVENTS because once these signals are recognized on a consistent basis, they turn on the NMDA receptors which then release prostaglandins and nitric oxide initiating the ENTIRE chain of events again in the adjacent neurons. And what that does is lowers the threshold for pain again, and they start firing spontaneously. UNTIL these pain signals can be turned off the patient will remain in this 'wind up mode' and could develop a complex pain syndrome." HealthSouth Pain Management Plan, April 19, 2001. PKY181246683 at 6851. Document is part of "OxyContin Files (HD)" which includes presentations and papers made by Purdue to HealthSouth re: adoption of their new pain management plan.

Comment: The statements above were misleading and detrimental to patients, for the following reasons. First, these statements represent the opioid sellers' efforts to increase prescribing by instilling fear of reprisal from the State Medical Boards

and/or The Joint Commission, as well as patients demanding opioids and complaining about their care. The message to prevent pain before it happens was leveraged to support the controversial idea that untreated pain can lead to centralizing pain disorders, which would not only leave acute pain untreated, but also risk a life-time condition if a centralizing pain disorder were to develop. Even if this centralizing pain phenomenon exists, opioids are the worst possible treatment, because these disorders are closely linked to depression and addiction, and the risks for such conditions are exacerbated by opioid therapy.

B. Risks of Opioids Understated

1. *Myth: Addiction is rare*

- “Realize that drugs and doctors do not cause drug addiction. Admit that withholding pain medication can be deleterious. Admit that true addiction is much less of a problem than presumed.” Purdue Physicians’ Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057 at 5080.
- Presentation by Dr. Melvin Gitlin at the Purdue Physician’s Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5156, in which he states, “Persuasive evidence that the use of opioid presents either a risk to the health of the individual or to society is lacking. Similar prejudices had been advocated to impede the opioid treatment of patients with malignant pains and are being overcome.”
- Presentation by Dr. Mary Stegman entitled “Pain Management in the Elderly Patient, Special Considerations,” for Purdue’s Physician’s Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at PKY181655169, in which she states “Myth: Opiates create addicts” outlining a study of 10,000 burn patients, 0 patients (0.00%) were addicted; another study of 25,000 patients, only 7 patients (0.03% patients) were addicted, concluding “Forget That Excuse!” As discussed in my Report, the studies to which she refers are non-representative samples in studies ill-designed to assess for misuse and addiction.

2. *Myth: The problem is the ‘addicts,’ not the drug*

- "Are Opioids Always Addictive? No! Watch out for cherry syrup addicts! Opioid addicts should not be given opioids without careful consideration of the circumstances." Accredited Pain Management Program for the Educator, April 3-6, 2000. PKY180775599 at 5650.

Comment: By using the term “cherry syrup addicts,” the author is presumably referring to patients with opioid addiction getting treated with methadone in liquid form from a methadone maintenance clinic. This pejorative usage is typical of the ways in which Purdue labeled and stigmatized people with opioid use disorder, and promoted the idea that by separating opioid addicted persons as a distinct population, the remaining patients could be prescribed opioids without risk.

- “Molecules don’t hook patients, patients with psychopathology take drugs to be fixed. Addicts want medications for wrong reason, trying to get high, not to have less physical pain.” Accredited Pain Management Program for the Educator, April 3-6, 2000. PKY180775599 at 5652.

Comment: This statement perpetuates the myth that ‘addicts’ are a separate category from ‘legitimate’ pain patients. The reality is that legitimate pain patients can and do get addicted through an opioid prescription.

3. *Myth: No dose is too high; optimal dose is determined by titrating upwards until analgesia*

- "No ‘ceiling’ to analgesic efficacy - may be titrated upward as necessary. With full agonists, such as oxycodone, ‘effectiveness with increasing doses is not limited by a 'ceiling'’." OxyContin Launch Plan, September 27, 1995. PURCHI-003286781 at 6804.
- "No maximum daily dose or ‘ceiling’ to analgesic efficacy. May be titrated every 1 to 2 days, if necessary. Common opioid side effects may be effectively managed- many, except constipation, diminish over time for most patients." OxyContin Advertising and Black Box Warnings, June 15, 1998. PKY180625450 at 5452.
- Presentation by Dr. Mary Stegman entitled “Pain Management in the Elderly Patient, Special Considerations,” for Purdue’s Physician’s Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5172, in which she states “Titrate to effectiveness not to milligrams.”

- "There are no standard opioid doses. Patients experience their pain uniquely. Dosages not consistent due to individual variations in pain intensity mechanisms of action. Patients need doses that relieve or modify the pain without toxicity. Milligrams Just Don't Matter...Milligrams are not the issue, pain control and absence of toxicity are the issues." Accredited Pain Management Program for the Educator, April 5, 2000. PKY180775599 at 5647.

Comment: The statements above are misleading because they omit that increased dose increases risk of dependence, addiction, and numerous adverse effects, including death.

4. *Myth: Dependence is not a significant problem and is easily reversible*

- "Now, when was the last time that you took a patient off insulin because their blood sugar had gotten to normal? Do you taper your patients off their antihypertensive when their blood pressure gets to normal? In primary care our assumption is that we're going to be treating people with chronic diseases for long-term, so why don't we do that with pain patients?" "Legal and Ethical Issues Affecting Pain Management", © 2001 a "Free CME" course "supported by an education grant from Purdue Pharma" and distributed by FamilyPractice.com and Purdue.. PKY180769094 at 9123,9095

Comment: Comparing opioids to insulin is a false analogy because insulin does not cause diabetes; whereas exposure to opioids causes opioid dependence, and in a subset, opioid addiction.

- "Addiction is a behavioral disorder of 'compulsive drug use, despite harm.' This has not been recorded as a result of the medical use of opioids. Opioids do cause physical dependence, i.e. there is a brief, flu-like withdrawal syndrome on suddenly stopping them. But this is not addiction, it is not dangerous and is easily avoided by tapering opioids over about 2 weeks. (By contrast, the withdrawal syndrome for benzodiazepines can be very dangerous, and very prolonged. Preventing it may require tapering over a period of several months.)" Purdue Physicians' Pain Management Speaker Training Program, April 18-20, 1997. PKY181654940 at 4966.
- Presentation from Dr. Neil Ellison at the Purdue's Physicians Pain Management Speakers Training Program in San Antonio, Texas on April 19, 1997: "Physical

dependence will occur in most patients regularly taking opioids for prolonged periods of time (usually greater than several weeks); however, if the cause of the pain is relieved, these patients can safely and rapidly be withdrawn completely by fractionating (usually by 1/3-1/2 their doses daily or every other day). The patient can usually discontinue completely without withdrawal symptoms..."

PKY181654940 at 4950.

Comment: Dependence and tolerance are serious physical conditions in themselves; they also lead to increased doses and addiction in a subset of patients, and to long, slow, and often failed attempts at tapering.

5. *Myth: Tolerance is rare - respond with higher dose*

- "(Despite different findings in experimental animals), a remarkable phenomenon is observed in the clinical setting. Loss of analgesia rarely occurs in patients with stable pain syndromes. Patients without progressive disease...typically achieve stable dosing that extends for a prolonged period. When the need for dose escalation occurs, an alternative explanation, typically worsening of the underlying disease, can usually be identified." Physicians' Pain Management Speaker Training Program, April 18-20, 1997. PKY181654940 at 4969, quoting Portenoy RK. In "Pain Management: Theory and Practice," ed. Portenoy Kanner, FA Davis Company, 1996: Chapter 11, p255.
- "Tolerance is defined as the need for increasing doses of medication to maintain the same effect. This is easily and reliably produced in animal models, yet is rarely seen in humans. In fact, in the case of cancer pain, what has thought to be tolerance has been shown to typically be disease progression necessitating the need for increased opioids to maintain comfort." Purdue Physicians' Pain Management Speaker Training Program, presentation by David Haddox April 18-20, 1997. PKY181654940 at 4962.
- "Although tolerance may occur in some cases, generally patients become tolerant to bothersome side effects more so than to analgesic effects. Evidence from cancer studies suggests that when patients clinically stable on a certain opioid dose, request a dose escalation, it may be more related to progression in their disease than to tolerance." Physicians' Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057 at 5092.

Comment: Tolerance is not “rare” in humans. It is common. Tolerance leads to increased dosage and increased risk.

6. *Myth: Pseudo-addiction – respond with more opioids*

- “[I]n the setting of undertreated pain, some patients develop aberrant behaviors that may be quite similar to those associated with addiction. When pain is relieved, the behaviors cease and opioids and other drugs are used responsibly.” Physicians’ Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057 at 5100.
- Types of Pseudoaddiction Behavior: “Hoarding; Concern about supply; May be going to multiple physicians and pharmacies; Drug-seeking behaviors common; First described in cancer patients.” Physicians’ Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057 at 5081.
- “Pseudoaddiction: appropriate drug seeking behavior demanding doses before they are scheduled; vicious cycle of anger, isolation, and avoidance leading to complete distrust. Weissman DE, Haddox DJ. Pain 1989;36:363-6. Increase the opioid dose by 50%, assure that breakthrough doses are available; complaints resolve when analgesia is established.” Physician’s Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5208. Haddox is now a Purdue Pharma VP of Health Policy. See Haddox ResearchGate Profile page at <https://www.researchgate.net/profile/J_Haddox> Accessed on January 25, 2019.
- “Pseudoaddiction Relative to Psychiatric Pain Consultations--Involves appropriate attempts to obtain medication to relieve pain. “Clock watching” behavior is indicative of under treatment of pain. We should believe patients unless evidence proves otherwise. Consider 50 to 100% dose increase to see if the behavior changes.” Accredited Pain Management Program for the Educator, August 5, 2000. PKY180775599-PKY180775707 at 5649.
- “...the more the patient insists on the need for stronger pain medicine, the more likely we are to withhold analgesia, on the grounds that this insistence shows ‘substance abuse’ for which the treatment is abstinence from the ‘offending substance’. We equate this ‘drug seeking behavior’ with addiction, and use it to justify further undertreatment or even complete withdrawal of analgesics. This further reinforces the patient’s desperate pursuit of pain relief. If this leads to

manipulativeness or frank deceit, the misdiagnosis of addiction is reinforced. Not only the doctors, but also the patient and family may conclude that the problem is drug addiction. This is called ‘pseudo-addiction,’ a term first defined by Weissman and Haddox.” From presentation “Control of Pain: Every Person’s Right ,” Pain Management Speaker Training Program for Physicians, May 5-7, 2000. PKY180170528 at 0545.

- “The distinction can usually be made quite simply. For a period of about a week, prescribe a substantially increased dose of opioid, preferably with a range of doses so that the patient can explore the optimum dose. The aim is to challenge the patient’s ability to shed drug-seeking behavior when adequate analgesics are available. Every day the patient records pain level, activities tolerated, and total pills taken. After a week, he/she brings the record to the physician, along with remaining pills. Ideally the partner should come also. If the problem is pseudoaddiction, the patient will be visibly more comfortable and refreshed; the partner will corroborate the patient’s account of improved activity tolerance; the daily pill count will be medically credible; and the remaining pill count will fit with the record. None of the aberrant behaviors listed above will have occurred: drug-seeking behavior has been extinguished at a stroke.” From “Control of Pain: Every Person’s Right” presentation, Pain Management Speaker Training Program for Physicians, May 5-7, 2000. PKY180170528 at 0545.

Comment: As detailed in the Report, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept.

Appendix I.B.: Teva/Cephalon

Teva/Cephalon Misleading Messaging

A. Benefits of Opioids Overstated

1. *Myth: Opioids are effective for chronic pain*

- “Opioid analgesics are another important class of medications that are very effective pain relievers As mentioned before, they may also be called ‘narcotics.’ Unfortunately, this term is used by law enforcement to refer to drugs that are abused. Cocaine and heroin are called narcotics even though they are very different kinds of drugs. Calling opioid analgesics ‘narcotics’ reinforces myths and misunderstandings as it places emphasis on their potential abuse rather than on the importance of their use as pain medicines.” American Pain Foundation Guide for People Living with Pain (TEVA_MDL_A_01090496 at 0514) The APF Guide discussed here and below was produced with the financial support of Cephalon and Purdue. (TEVA_MDL_A_01090496 at 0499) KOL’s Scott Fishman and Russell Portenoy were named as physician reviewers and members of APF’s Board of Directors. (TEVA_MDL_A_01090496 at 0501) Fishman and Portenoy also provided testimonials for the APF Guide, calling it a “must have” and “a very good resource” for chronic pain patients. (TEVA_MDL_A_01090496 at 0579)

Comment: This quote summarizes the essential message promoted by Teva/Cephalon in a patient-facing document that promoted misleading messages under the guise of education. The authors describe non-opioid medications such as Tylenol and NSAIDs as “effective for mild to moderate pain,” but never as “very effective pain relievers,” a phrase reserved for opioids. Indeed the sections on NSAIDs and Tylenol emphasize the risks of these drugs. By contrast, when the authors detail opioids, the risks are underplayed, as in this statement in which heroin is called a “very different kind of drug,” even though the only difference between heroin and morphine is two acetyl groups, and prescription opioids are as addictive as heroin. Indeed heroin and morphine are very similar drugs, yet are portrayed here as different to mislead readers as to the addictive potential of prescription opioids.

- “Despite the great benefits of opioids, they are often under-used. For a number of reasons, providers may be afraid to give them and the public may be afraid to take them. Some feel opioids should not be used to treat persistent pain except in persons who are dying. Others are concerned that the average person will become

addicted to these drugs. These concerns lead to confusion and hesitation on the part of some providers to prescribe these for pain control. Adding to the problem is the increase in abuse of prescription drugs in the U.S. Persons with addictive disease (in the past, the term ‘addicts’ was used) have obtained and misused these drugs. Others have taken them illegally through pharmacy thefts or under false pretenses in order to sell them ‘on the street’ for profit.” American Pain Foundation Guide for People Living with Pain (TEVA_MDL_A_01090496 at 0514-5)

Comment: The authors claim “great benefits of opioids.” In fact, there is no reliable evidence that opioids are effective treatment for chronic pain, or what authors here describe as “persistent pain.” Further, there is abundant evidence that opioids taken long term (greater than 3 months) incur considerable and life-threatening harms. Yet the authors suggest that “confusion and hesitation” on the part of prescribers is unfounded. They then go on to suggest that the current opioid crisis is a result of “addicts,” a stigmatizing term they use for supposed historical clarification, to imply that “addicts” are the source of the current opioid epidemic. In fact, increased access to opioids through the Defendants’ misleading marketing is the primary culprit, making the public more vulnerable to opioid addiction.

2. *Myth: Opioids are first-line treatment for all types of pain*

- “Opioids are an essential option for treating moderate to severe pain associated with surgery or trauma, and for pain related to cancer. They may also be an important part of the management of persistent pain unrelated to cancer. These medicines block pain messages in the body, but they also affect the way we feel about our pain and help us better tolerate it. Our body produces natural opioids (endorphins) as part of its survival response to danger and injury. Because the medications of this class work in the same way as endorphins, they work very well in blocking pain.” American Pain Foundation Guide for People Living with Pain (TEVA_MDL_A_01090496 at 0514)

Comment: By calling opioids an “essential option,” the authors are suggesting that opioids are necessary to treat different types of pain. By introducing the concept of “natural opioids,” the authors are further trying to make a link between prescription opioids and something that is “natural” and thereby safer or necessary. Again they introduce the statement “they

work very well in blocking pain,” to suggest their superiority compared to other pharmacologic strategies. In fact, head-to-head trials show that opioids are no better than Tylenol in the treatment of chronic pain, and incur more risks. Further, these statements do not distinguish between acute pain and chronic pain. While there was reliable evidence of efficacy of opioids for acute pain, as noted above and in the Report, there is no reliable evidence of efficacy for chronic, non-cancer pain. It is misleading to make a blanket statement of efficacy without making this distinction clear.

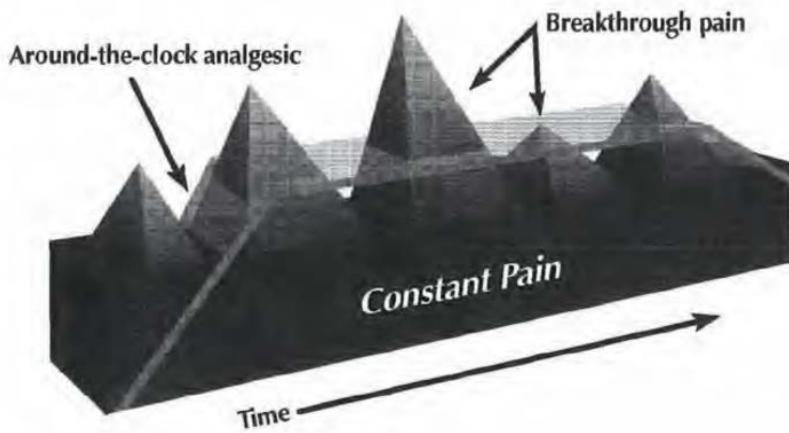
- “Targeting (APM, PM&R, RHU, N, ONC, PCP)” in sales presentation A Manager’s Perspective on Actiq (TEVA_MDL_A_09062111 at *13, produced natively)

Comment: Note here how marketing materials targeted many types of pain and pain providers, including “PCPs” [Primary Care Physicians], contributing to the paradigm shift away from using opioids rarely in specialty care, to using opioids as first line treatment in primary care.

3. ***Myth: Breakthrough Pain is a distinct clinical phenomenon that should be treated with opioids (rather than an artifact of tolerance and withdrawal in patients on long-term opioids).***

- “Breakthrough Pain. Breakthrough pain occurs on a background of otherwise controlled persistent pain; it is distinct from uncontrolled pain. Breakthrough pain is described as a transitory exacerbation or flare of moderate to severe pain in patients with otherwise stable persistent pain who are receiving chronic opioid therapy. In one study, the median duration of breakthrough pain was about 60 minutes. Breakthrough pain tends to be the most intense pain. Figure 6 illustrates this type of pain. Payne, 2007, S3; Portenoy, 2006, 586; Davis, 2004, 629.” Fentora Introduction to Pain (TEVA_MDL_A_00890305 at 0334). Figure 6 is

reproduced below:



- “Fentanyl is also available in a lozenge. In this formulation, it has a quick onset and short duration of effect that makes it especially useful for the treatment of ‘breakthrough’ pain.” American Pain Foundation Guide for People Living with Pain (TEVA_MDL_A_01090496 at 0516)
- “Breakthrough pain is often managed by adding a medication in addition to the drug used for the persistent pain. [Payne, 2007, S4-S5; Duragesic, 2008, I]” Fentora Introduction to Pain (TEVA_MDL_A_00890305 at 0335)
- “Third, frequent pain reassessment will help gauge the effectiveness of analgesic therapy. Assessment may help health care professionals choose more effective agents, titrate the dose or dosing interval appropriately, check the usefulness of the current route of administration, manage side effects, and assess the need for more effective breakthrough pain medication alongside the around-the-clock medication. [Carver. 2005, 10-11; McCarberg, 2007, S8]” Fentora Introduction to Pain (TEVA_MDL_A_00890305 at 0341)
- “ACTIQ is fentanyl in a unique oral transmucosal delivery system that provides the most rapid onset of analgesia of any non-invasive opioid formulation available which makes it the ideal agent for BTP or rapid onset pain, such as BTCP.” 2005 ACTIQ Marketing Plan

(TEVA_CAOC_00759630 at 9675) (ACTIQ 2005 Positioning Statement, emphasis in the original)

- “2005 Key Marketing Issues and Strategies: The overall marketing strategy for 2005 will continue to build on the platform developed in previous years, which will be to raise awareness of BTCP and ACTIQ and differentiate ACTIQ from its competitors by educating clinicians about the core product benefits (rapid onset of analgesia, portability, convenience and patient controlled administration). The key marketing issues facing ACTIQ in 2005 that must be addressed include providing the sales force with effective tools as well as providing them with optimal messages for key targets; ensuring a smooth transition to sugar free ACTIQ; increasing awareness in assessing and treating BTCP; and addressing the fears and concerns surrounding opioids. Also, growing managed care issues must be addressed as well as increasing and improving Key Opinion Leader (KOL) relationships.” 2005 ACTIQ Marketing Plan (TEVA_CAOC_00759630 at 9633)
- “The goals are to maximize ACTIQ sales until patent expiry with focused sales efforts on specific targets and to ensure that any efforts toward establishing BTP can also be leveraged for OVF” [Teva OraVescent® containing fentanyl product]. 2005 ACTIQ Marketing Plan (TEVA_CAOC_00759630 at 9674)

Comment: Teva/Cephalon promoted the idea of “breakthrough pain” as a physiologic phenomenon, when in fact it is a made up term to explain the loss of opioid efficacy when taken long term, due to tolerance and withdrawal. Promoting the idea of breakthrough pain as a legitimate medical phenomenon was advantageous for Defendants, because they could then promote their products as “treatment” for breakthrough pain. Actiq and Fentora were aggressively promoted as treatment for breakthrough pain.

4. *Myth: Not using opioids is tantamount to undertreating pain, is hence immoral, and may make pain worse in the long run.*

- “Obviously, it is very important to get the facts about these effective and powerful pain medicines because their under-use has been responsible for much unnecessary suffering. Those affected by pain, providers, patients and family alike, need to be well-informed to be sure that myths and

misunderstandings do not get in the way of effective pain control.”
American Pain Foundation Guide for People Living with Pain
(TEVA_MDL_A_01090496 at 0515)

Comment: Such statements are misleading and detrimental because they suggest to patients that doctors who are not prescribing opioids are not doing their job and indirectly causing suffering by withholding opioids. In fact, withholding opioids to a person in pain may be shielding them from long-term harms. Further, this fact has been known well before Defendants launched their misleading marketing campaign. A paper published in a peer reviewed medical journal in 1954 had this to say about prescribing opioids for pain, “Morphine is not the answer to chronic pain. Because of the development of tolerance to the analgesic effects of morphine, alleviation of pain becomes inadequate. Under such circumstances the physician, by gradually withdrawing narcotics, does not deprive the patient of any actual benefit but protects him and his family from the possible legal, social, or economic difficulties attendant on opiate addiction. The administration of morphine to a patient with chronic pain is a short-lived type of kindness. Long-term kindness would begin when opiates are withheld or withdrawn in favor of other therapeutic measures.” Rayport M. Experience in the Management of Patients Medically Addicted to Narcotics. *JAMA*, 1954:684-691, at p. 690.

- “Physicians often undertreat pain due to a lack of education about pain. This results in an inadequate pain assessment and less than optimal treatment, such as use of nonsteroidal analgesics for severe pain.” Fentora Introduction to Pain (TEVA_MDL_A_00890305 at 0350)

Comment: This statement suggests that not prescribing opioids is tantamount to not treating pain, ignoring the fact that even limited exposure to opioids is risky, and that many studies show comparable efficacy between opioids and other forms of pain treatment, with much less risk for non-opioid medications.

B. Risks of Opioids Understated

1. *Myth: Addiction is rare*

- “Family members/caregivers may worsen patient concerns and fears about analgesic use. Caregivers may lack information about proper pain management and its benefits. Like patients, caregivers may need reassurance that few people using opioids for a legitimate medical reason become addicted to the drug, and that physical dependence to a drug is easily overcome through scheduled dosing decreases, if the patient improves to the point where opioids are no longer needed... [Willis, 2007, 261- 262; AACPI, 2004, 6-7]” Fentora Introduction to Pain (TEVA_MDL_A_00890305 at 0346)
- “Patients can also inhibit therapy by refusing to take pain medications or by taking them inappropriately. Patients may hear descriptions of physical dependence about certain medications (opioids) and fear the stigma or behaviors they associate with drug addicts - behaviors that are not common in patients without previous history of addiction. Patients may believe that analgesics should be ‘saved’ until the end of life so that they are effective then; patients may need reassurance that an appropriate dosage of opioid will be available as pain increases, and they need not suffer now to avoid analgesic tolerance in subsequent disease stages. [Carver, 2005, 10-11,Gunnarsdottir, 2003, 426, Willis, 2007, 261]” Fentora Introduction to Pain (TEVA_MDL_A_00890305 at 0345)
- “Pain appears to reduce the euphoric effects of opioids, so people taking opioids to manage their pain may be at a lower risk for addiction. [APA, 2005, 2]” Fentora Introduction to Pain (TEVA_MDL_A_00890305 at 0355)
- “Less potential for abuse” in sales presentation A Manager’s Perspective on Actiq (TEVA_MDL_A_09062111 at *10, produced natively)

Comment: The authors misleadingly convey that the risk of opioid misuse and addiction is low if patients with pain are prescribed opioids by their doctors. In fact, reliable evidence shows that one in four chronic pain patients prescribed opioids will develop an opioid misuse problem, and one in ten will become addicted to opioids. Further, these risks were known before Defendants began the aggressive marketing campaign. As to

the assertion that behaviors indicating addiction are “not common in patients without a previous history of addiction,” Edlund et al’s 2014 study shows that the largest contributor to risk of addiction is dose and duration (OR = 122 for opioid doses over 120 MMEs for 3 months or longer), a far more impactful risk than personal history of addiction (OR 3-9). (Edlund MJ, *et al.* The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain. *Clin J Pain.* 2014;30:557-564 at p. 557.) It is false to equate feeling “euphoria” from opioids as a marker of addiction. Many people who get addicted to opioids do not endorse feeling euphoric from opioids. Indeed, many describe pain relief as the initial driver. Further, once people become addicted to opioids, they stop feeling euphoric effects. Instead they’re compelled to continue consuming opioids just to feel normal and avoid the pain of withdrawal.

- “The most common side effects of opioids include constipation, nausea and vomiting, sedation (sleepiness), mental clouding and itching. Some people may also experience dizziness or difficulty urinating. Respiratory depression, a decreased rate and depth of breathing, is a serious side effect associated with overdose. The good news is that most side effects go away after a few days.” American Pain Foundation Guide for People Living with Pain (TEVA_MDL_A_01090496 at 0517)

Comment: In this patient-facing educational material, the risk of addiction is underplayed, not mentioned once in the section subheading “Most Common Side Effects.” Yet according to World Health Organization classification of risk, the risk of addiction to prescription opioids is “common” to “very common”: one in four persons prescribed an opioid for chronic pain will develop an opioid misuse problem, and at least one in ten will become addicted.

- “Usually has a friend who was addicted to fentanyl in med. school, failed out and is an addict? It's amazing how often it happens??” Actiq Physician Segmentation Guide (TEVA_MDL_A_01327081 at 7082)

Comment: This was from a sales training document to train sales specialists how to approach doctors who are more “cautious” in their opioid prescribing habits. The casual disregard for a personal exposure to addiction is consistent with a corporate culture in which every indication

of the serious risks of addiction is framed as a sales obstacle to be overcome with marketing tactics. Further, this statement reveals that corporate executives fully understand the high prevalence of addiction to fentanyl products: “amazing how often it happens??”

2. *Myth: The problem is the “addicts,” not the drug*

- “Others are concerned that the average person will become addicted to these drugs. These concerns lead to confusion and hesitation on the part of some providers to prescribe these for pain control. Adding to the problem is the increase in abuse of prescription drugs in the U.S. Persons with addictive disease (in the past, the term ‘addicts’ was used) have obtained and misused these drugs. Others have taken them illegally through pharmacy thefts or under false pretenses in order to sell them ‘on the street’ for profit.” American Pain Foundation Guide for People Living with Pain (TEVA_MDL_A_01090496 at 0515)

Comment: By implying that the “average person” need not fear addiction to prescribed opioids, and that the U.S. opioid crisis is the result of “Persons with addictive disease” who “obtained and misused these drugs,” the authors are suggesting that the addiction exists before the individual is prescribed opioids, excluding the possibility that a patient could become addicted through a prescription. With this misleading messaging, authors are perpetuating the myth that “legitimate” pain patients prescribed an opioid from a doctor can’t get addicted. In fact, as referenced in my Report, the CDC and the Director of NIDA the Report, Nora Volkow, have stated that anyone can become addicted to prescription opioids, and sources such as the ASPPH confirm that the opioid epidemic was fueled by the oversupply of prescription opioids. This misleading messaging further promotes the idea that by separating opioid-addicted persons as a distinct population, the remaining patients can be prescribed opioids without risk. The reality is that legitimate pain patients can and do get addicted through an opioid prescription.

- “Opioids get into the hands of drug dealers and persons with an addictive disease as a result of pharmacy theft, forged prescriptions, Internet sales, and even from other people with pain. It is a problem in our society that needs to be addressed through many different approaches.” American Pain

Foundation Guide for People Living with Pain
(TEVA_MDL_A_01090496 at 0518)

Comment: Although it is true that diversion of prescription drugs is an important factor in this opioid epidemic, it is also true that people misuse, overuse, get addicted to, and die from prescription opioids received directly from their doctor to treat a medical condition. This statement is misleading because it implies that only people engaging in illegal activity are at risk. In fact, anyone exposed to an opioid for any reason is at risk.

3. *Myth: No dose is too high; optimal dose is determined by titrating upwards until analgesia*

- “The other opioids can relieve severe pain. Their doses can be gradually increased over time. There is no ceiling dose as there is with the NSAIDs. As pain worsens, these medications continue to be useful unless side effects occur. It is a myth that opioids, like morphine should only be used at the final stages of a seriously painful disease. When pain is severe, opioids should be considered.” American Pain Foundation Guide for People Living with Pain (TEVA_MDL_A_01090496 at 0515)

Comment: Statements like these are misleading because they ignore that risks of opioids increase with increasing dose, and that many organs are adversely affected by opioids, not least of all the brain. Increasing doses can lead to the risks of tolerance, dependence, withdrawal, addiction, depression, cognitive impairment, and numerous other adverse effects, including risk of overdose and death.

4. *Myth: Dependence is normal, not a significant problem, and easily reversible.*

- “Physical dependence means that a person will develop symptoms and signs of withdrawal (e.g., sweating, rapid heart rate, nausea, diarrhea, goosebumps, anxiety) if the drug is suddenly stopped or the dose is lowered too quickly. Physical dependence is normal; any patient who is taking an opioid on a regular basis for a few days should be assumed to be physically dependent. This does NOT mean you are addicted. In fact, many non-addictive drugs can produce physical dependence. To prevent withdrawal from occurring, the dose of the medication must be decreased

slowly.” American Pain Foundation Guide for People Living with Pain (TEVA_MDL_A_01090496 at 0517)

Comment: Comparing dependence on opioids to dependence on non-addictive drugs is a false analogy because opioids work on the brain’s reward pathway and are therefore reinforcing beyond their pain-relieving properties. Further, there is significant overlap between those who become dependent on opioids and those who become addicted to opioids, and this statement minimizes that significant overlap.

- “Family members/caregivers may worsen patient concerns and fears about analgesic use. Caregivers may lack information about proper pain management and its benefits. Like patients, caregivers may need reassurance that few people using opioids for a legitimate medical reason become addicted to the drug, and that physical dependence to a drug is easily overcome through scheduled dosing decreases, if the patient improves to the point where opioids are no longer needed. Because caregivers play an integral role in therapeutic success, it may be helpful for health care providers to educate both patients and their caregivers about pain management programs in a joint discussion. [Willis, 2007, 261-262; AACPI, 2004, 6-7]” Fentora Introduction to Pain (TEVA_MDL_A_00890305 at 0346)

Comment: Dependence and tolerance are serious physical conditions in themselves and are not, as the authors state, always “easily overcome through scheduled dosing decreases.” See Weimer et al regarding the great difficulty many opioid-dependent patients have with tapering opioids. (Weimer MB, et al. A chronic opioid therapy dose reduction policy in primary care, *Substance Abuse*, 2016;37:1,141-147,)

5. Myth: Pseudo-addiction – respond with more opioids

- “Certain behaviors are sometimes mistaken for addiction. If patients receive inadequate pain relief, they may exhibit drug-seeking behaviors. This is called pseudoaddiction. When these patients receive adequate pain management, they no longer exhibit the same behaviors. Patients in pain do not usually become addicted to opioids. [Kahan, 2006, 1082-1083; NPC and JCAHO, 2001, 17]” Fentora Introduction to Pain (TEVA_MDL_A_00890305 at 0355)

Comment: As detailed in the Report, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue. A review article found that there was no empirical evidence to support such a diagnosis, and that impartial scientists have criticized its usage, whereas authors affiliated with the opioid sellers have advocated the concept. Greene MS, Chambers RA. Pseudoaddiction : Fact or Fiction ? An Investigation of the Medical Literature. *Curr Addict Rep* 2015:310-317. doi:10.1007/s40429-015-0074-7.

Appendix I.C: Janssen

Janssen Misleading Messaging

A. Benefits of Opioids Overstated

1. *Myth: Opioids are effective for chronic pain*

- “Effective Pain Relief Improves Physical Function In Patients With Chronic Pain. Patients with chronic low back pain receiving opioid analgesia reported significantly greater reduction in pain intensity and improved exercise performance vs patients receiving placebo.” Chronic Pain Management Message Platform, August 20, 2009. JAN-MS-00068759- JAN-MS-00068828 at 8798

Comment: This quote is misleading because it is part of a “Chronic Pain Message Platform,” but it relies on short-term studies to support claims of long-term pain relief. There are not now and have never been any reliable scientific studies showing efficacy of opioids for chronic pain.

2. *Myth: Opioids are first-line treatment*

- “Duragesic: A First-Line Choice for Chronic Around-the-Clock Opioid Therapy. Consider as first-line for patients with moderate-to-severe chronic pain who require continuous opioid analgesia: Degenerative joint disease; Chronic back pain; Cancer pain; Has been shown to be effective in certain cases of chronic neuropathic pain.” Optimizing Chronic Pain Management with Duragesic, December 14, 2001. JAN-MS-00653403, at *19 (produced natively).

Comment: By not distinguishing between cancer pain and non-malignant pain, or between acute and chronic pain, the statement is misleading, in that there was no reliable evidence that opioid therapy was effective for chronic, non-malignant pain. A similarly misleading statement appears in the 2007 DURAGESIC Patient Brochure for pain expected to last for “weeks or longer,” stating that DURAGESIC has been used “for more than 16 years to effectively relieve pain,” yet citing, as support for that claim, a 1995 article written by an industry employee that states, “Clinical trials have established the efficacy and safety of transdermal fentanyl for the treatment of cancer pain. Transdermal fentanyl is not licensed for the treatment of acute pain, e.g. postoperative pain, and should not be prescribed for this purpose.” JAN00222296_POT-01DR1050AR2.pdf, at

pp. 7, 28; citing Southam, “Transdermal fentanyl therapy: system design, pharmacokinetics and efficacy,” Anticancer Drugs 1995; 6:29-34, at 29.

3. ***Myth: Opioids improve function and quality of life***

- “...we have enhanced our current promotional message to maximize our product benefits and address relevant issues among chronic pain physicians...research shows: 1) functionality is a key driver of brand selection, 2) functionality is the end-benefit of physician treatment goals and 3) no brand owns functionality.” Duragesic Market Update, July 3, 2002. JAN-MS-00310227 at 0228.
- Janssen’s *Let’s Talk Pain* website states that the use of opioids for the treatment of chronic pain can lead to patients regaining functionality and features an interview claiming that opioids were what allowed a patient to “continue to function.” *Resources for Pain Management: Understanding Tolerance, Physical Dependence and Addiction*, Let’s Talk Pain, https://web.archive.org/web/20120322234928/http://www.letstalkpain.org/real_story/addictions.html.
- Janssen’s patient education guide *Finding Relief* states that opioids can make it possible for people with chronic pain to “return to normal, e.g., to get back to work, walk or run, play sports, and participate in other activities.” JAN-MS-00829901 at JAN-MS-00829910.
- A consumer webcast video for Ultram ER contained the statement “Because my chronic pain was waking me up throughout the night, I worked with my doctors and found a medication called Ultram ER, that provides management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time. Ultram ER not only helped to manage my chronic pain, but because Ultram ER is a 24-hour treatment, I no longer found myself waking up due to chronic pain. This was and is important to my overall chronic pain management program, because sleep is a critical factor in my overall mood, which affects my relationships.” ENDO-OPIOID_MDL-03850803 at 0806.

Comment: The FDA reprimanded Janssen for its “quality of life claims,

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including but not limited to, ‘And the #1 reason to convert your patients to the Duragesic patch: QUALITY OF LIFE,’ and ‘. . .without pain, patient’s sleep better, increase daily activities, and spend more quality time with their families.’ Health related quality of life claims such as these require substantial supporting evidence in the form of adequate and well - controlled studies designed to specifically assess these outcomes. Therefore, without substantiation from adequate studies, the claims presented in this ‘homemade’ promotional piece are misleading.” FDA Letter to Janssen RE: NDA 19-813, March 30, 2000. JAN-MS-00238338 at JAN-MS-00238341, *see also* at JAN-MS-00238344- JAN-MS-00238345. There was a further FDA reprimand for the webcast video because it “misleadingly implies that patients treated with the drug will experience an improvement in their sleep quality. The webcast cites no support of these claims and there is neither evidence nor substantial clinical experience to support this effect of Ultram ER. FDA Warning Letter. RE: NDA 21-692, ENDO-OPIOID_MDL-03850803. There is no reliable evidence to date that opioid pain medications improve long-term function or quality of life.

B. Risks of Opioids Understated

1. *Myth: Addiction/abuse is rare/low/uncommon/less than 1%*

- “In 10 years of use, low and stable reported rate of abuse.” Optimizing Chronic Pain Management with Duragesic, December 14, 2001. JAN-MS-00653403, at *17 (produced natively).
- “Iatrogenic addiction from opioid analgesia in patients experiencing pain is exquisitely rare. The Boston Collaborative Drug Surveillance Program study revealed only four cases of iatrogenic addiction among 11,882 patients without a prior history of substance abuse who received opioids for a broad range of indications.” Opioidphobia PowerPoint, August 1, 2001. JAN-MS-00653426, at *25 (produced natively).
- “[P]atients may have concerns: ‘I’m afraid I’ll become a drug addict.’ Addiction is relatively rare when patients take opioids appropriately.” Duragesic Website Pages, April 10, 2006. JAN00222151, at *89 (produced natively).

- “Problematic Opioid Analgesic-Related Behavior Reported In An Evidence-Based Review Was Low. Structured evidence-based review on abuse/addiction and aberrant drug-related behaviors (ADRBs) in patients with chronic pain receiving chronic opioid analgesia. Abuse/addiction rate of 3.27% (24 studies, N = 2,507). Amongst patients with no previous or current history of abuse/addiction, the rate was 0.19%. ADRB rate was 11.5% (17 studies, N = 2,466). Among patients with no previous or current history of abuse/addiction, the rate was 0.59%.” Chronic Pain Management Message Platform, August 20, 2009. JAN-MS-00068759-JAN-MS-00068828 at 8811, citing Fishbain et al. Pain Med. 2008; 9:444.
- “[S]tudies indicate that the de novo development of addiction when opioids are used for the relief of pain is low.” Duragesic Information on Opioid Dependence, Tolerance and Addiction, 2002. JAN-MS-00303825, at *2 (produced natively), referencing Definitions Related to the Use of Opioids for the Treatment of Pain: A Consensus Document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine.
- “Given the relatively decreased potential of misuse of long-acting (*e.g.*, methadone) and sustained-release opioids (*e.g.*, transdermal fentanyl) in chronic pain patients, these may be preferred over short-acting opioids.” Speakers Notes, Assessing Risk of Substance Abuse, 2002. JAN-MS-00310473 at *18 (produced natively).
- Speaker’s notes from a Janssen sales training presentation cite to Joranson (2000) to state that “investigators concluded that the trend of increasing medical use of opioid analgesics to treat pain does not appear to contribute to increases in the health consequences of opioid use.” JAN-MS-00302787, at *29 (produced natively).
- Janssen’s *Prescribe Responsibly* website states that concerns about opioid addiction are “often overestimated,” and that “true addiction occurs in only a small percentage of patients.” Keith Candiotti, M.D., *Use of Opioid Analgesics in Pain Management, Prescribe Responsibly*, <http://www.prescriberesponsibly.com/articles/opioid-pain-management>.

- Janssen's *Prescribe Responsibly* website states: "In those cases when a patient expresses concern about addiction," it is important to have a further discussion, because if the concern turns out to fall within the technical definition of "physical dependence," the patient's addiction concerns can be overcome by "reassurance from the healthcare professional." Keith Candiotti, M.D., *Use of Opioid Analgesics in Pain Management, Prescribe Responsibly*, <http://www.prescriberesponsibly.com/articles/opioid-pain-management>.
- Janssen's patient education guide *Finding Relief* dismisses as "myths" the facts that opioids are addictive, can make functioning more difficult, and often must be prescribed in higher doses over time. JAN-MS-00829901, at JAN-MS-00829910.
- Janssen's *Prescribe Responsibly* website states that addiction risk screening tools allow HCPs to identify patients predisposed to addiction, thereby allowing prescribers to manage the risk of opioid addiction in their patient populations. Keith Candiotti, M.D., *Use of Opioid Analgesics in Pain Management, Prescribe Responsibly*, <http://www.prescriberesponsibly.com/articles/opioid-pain-management>.
- Janssen regarded the *Let's Talk Pain* and *Prescribe Responsibly* websites as integral to the launch of Nucynta ER. JAN-MS-00015864 at JAN-MS-00015878.
- Presentation for a Janssen unbranded campaign promoted as one of the "Key messages": "Although many physicians are reluctant to prescribe controlled substances, the risks (for both patient addiction/misuse, and physician disciplinary action) are much smaller than commonly believed." JAN-TX-00002318 at slide 13. The presentation also provided this "Execution tip": "Avoid the Addiction Ditch...Use Portenoy's study to create dialogue about Opiophobia as a barrier...Many HCP's will find the 2.6% incidence of addiction to be extremely low." JAN-TX-00002318 at slide 14.
- A Janssen sales training document proposed sample language to use on calls to prescribers, "it is a common misconception that the incidence of addiction and misuse is high when patients are prescribed an opioid. The

reality is, according to Dr. Portenoy's landmark registry study, behavior suggestive of misuse was seen in only 2.6% of patients. In addition, many physicians fear that if they prescribe opioids for too many of their patients, they might be subject to disciplinary action by their state medical boards. The reality is that only a tiny percentage of disciplinary actions have anything at all to do with controlled substances, and none of them were solely concerned with overprescribing." JAN-MS-01135846 at 5852.

Comment: As detailed in the Report, addiction is common among patients treated with opioids (10-30% of patients treated with opioid pain medication will develop an opioid use disorder/addiction), and the risk of addiction increases with increasing dose and duration. Studies quoting low rates of addiction were methodologically flawed and biased by drug company sponsorship. The Porter and Jick letter was not relevant to addiction resulting from chronic opioid therapy. The Fishbain reference did not disclose that Fishbain was an expert witness for an opioid seller (Purdue); did not disclose that Fishbain had written an earlier review that reported addiction rates as high as 18.9%; and did not disclose the numerous flaws in the Fishbain 2008 article described in the Report. The reference to Joranson did not disclose that Purdue financially supported Joranson's Pain and Policy Studies Group (WIS_PPSG_008286) , and did not disclose that by 2004 even Joranson had published an updated report documenting substantially increased Emergency Department admissions for the period 1997-2002, compared to the period 1990-1996 covered by his previous article. ("In 2002, opioid analgesics accounted for 9.85% of all drug abuse, up from 5.75% in 1997." Gilson, Ryan, Joranson and Dahl, *J Pain Symptom Manage.* 2004 Aug; 28(2):176-88.). Portenoy, assessing Oxycontin misuse/addiction, used a questionable denominator with 133 patients dropping out, excluded patients with self-reported past or present substance or alcohol abuse, and was sponsored by Purdue. Portenoy, *et al.*, Long Term Use of Controlled-release Oxycodone for Noncancer Pain: Results of a 3-year Registry Study. *Clin. J. Pain* 2007; 23: 287-299, DOI: 10.1097/01.brs.0000186860.23078.a8.

2. ***Myth: No dose is too high***

- Emails to district sales managers pushed higher dosage messaging for Ultram ER: "Focused message geared toward 200[mg]- get out of the 'letter of the law' mentality (ie-stop the state w/ 100[mg] for opioid naïve

patients and just say other Dr.’s are having success starting at 200mg)” JAN-TX-00053505.

- Emails to sales representative and managers pushed a high dosage message: “We also discussed the importance of sampling- save the titration packs for the primary care physicians and the 200mg bottles for the specialists. Our goal is to get the patient to start on 200 mg or more if they need to titrate up. ‘Doctor, why would you start a patient on a minimal dosage of tramadol when your patient is in pain. The minimum dose of tramadol IR would be 200-400kmg daily...So, you need to start the patient on 200mg.’ The beauty of Ultram ER is the flexibility in dosing. We cannot flinch on the sale for fear of side effects.” JAN-TX-00277835 at 77836.
- “Doctor, there is no established ceiling dose for Nucynta ER” and “Note to Sales Representatives: A ceiling dose is the threshold at which additional dose increases produce no change in efficacy and often lead to greater side effects. It is a plateau effect that is common to most medications. However, it is important to note that pure opioid agonists, such as morphine, do not have a ceiling dose.” Nucynta ER Frequently Asked Questions, November 17, 2011. JAN-MS-00016372-JAN-MS-00016397 at 6379.
- “In your practice you may titrate your patients at your discretion, based on your assessment of their pain management needs.” Nucynta ER Frequently Asked Questions, November 17, 2011. JAN-MS-00016372-JAN-MS-00016397 at 6380. “There is no ceiling dose for opioids. Titrate the dose upward to obtain maximum pain relief without unacceptable side effects. Always prescribe rescue medication for breakthrough pain.” Optimizing Chronic Pain Management with Duragesic, December 14, 2001. JAN-MS-00653403, at *26 (produced natively).

Comment: The statements and messaging above are misleading because they omit that increased dose increases risk of adverse side effects, including but not limited to dependence, addiction, and death. The statement, “We cannot flinch on the sale for fear of side effects,” in the context of upselling higher doses, gives rise to particular concern, since it shows awareness of the accompanying increased risk, yet nevertheless

promotes the higher dose.

3. Myth: Dependence is not a significant problem and is easily reversible

- “Opioids can be discontinued in dependent patients without withdrawal difficulties by simply tapering them over about a week.” Opioidphobia PowerPoint, August 1, 2001. JAN-MS-00653426, at *24 (produced natively).
- “Physical dependence may be managed by gradually reducing the dose of the medication if the patient’s physician decides it is appropriate to discontinue therapy.” Duragesic Information on Opioid Dependence, Tolerance and Addiction, 2002. JAN-MS-00303825, at *1 (produced natively), (citing Passik SD, Portenoy RK, Ricketts PL. Substance abuse issues in cancer patients: part 1: prevalence and diagnosis. *Oncology*. 1998; 4:517-521).

Comment: Dependence and tolerance are serious physical conditions in themselves, leading to increased doses and addiction in a subset of patients, and to long, slow, and often failed attempts at tapering. “Tapering them over about a week” would cause extreme suffering in the majority of patients on chronic opioid therapy, and may even lead some to experience suicidal thoughts and/or turn to illicit sources of opioids.

4. Myth: Tolerance – Respond with higher dose

- “Tolerance does not mean that the medication has lost its effectiveness. Rather, the dose must be adjusted to achieve an effective level of pain relief.” Duragesic Information on Opioid Dependence, Tolerance and Addiction, 2002. JAN-MS-00303825, at *2 (produced natively).
- “Increases in opioid doses may be required over the first few days or weeks of therapy during titration to response. Tolerance to opioid analgesia typically does not occur once an effective dose of opioid is identified and administered regularly.” Opioidphobia PowerPoint, August 1, 2001. JAN-MS-00653426, at *26 (produced natively).
- “Tolerance rarely ‘drives’ dose escalation. Tolerance does not cause addiction.” Assessing the Risk For Substance Abuse, 2002. JAN-MS-00310473, at *8 (produced natively).

Comment: These statements are misleading, because tolerance is

common, is associated with addiction, and is in fact one of the DSM-5 criteria for addiction.

5. Myth: Pseudo-addiction –Respond with more opioids

- “Pseudoaddiction is a term used to describe patient behavior that can occur when pain is under-treated. Patients with unrelieved pain may become focused on obtaining medications and may seem to inappropriately seek drugs.” Duragesic Information on Opioid Dependence, Tolerance and Addiction, 2002. JAN-MS-00303825, at *2 (produced natively), (citing Savage S, et al.)
- “Pseudoaddictive behaviors mimic those of true addiction, but in reality may reflect undertreatment. This may include drug-seeking behavior, taking larger than prescribed doses, and running out of medications prematurely, tolerance, and withdrawal. Although adequate pain relief should eliminate the abnormal behavior if it is truly pseudoaddictive, it is important to recognize that pseudoaddiction and addiction can coexist.” Speaker’s Notes, Assessing the Risk For Substance Abuse, 2002. JAN-MS-00310473, at *1(produced natively) (citing Passik *et al.* 2000, p 73; Portenoy *et al.* 1997, p 563.)
- “Pseudoaddiction: Syndrome of abnormal behavior resulting from undertreatment of pain that is misidentified by the clinician as inappropriate drug-seeking behavior. Behavior ceases when adequate pain relief is provided. Not a diagnosis; rather, a description of the clinical intention.” Addressing the Barriers to Effective Pain Management and Issues of Opioid Misuse and Abuse, 2013. JAN-MS-01509021, at *19 (produced natively).
- Janssen’s *Let’s Talk Pain* website describes the concept of “pseudoaddiction” as “patient behaviors that may occur when pain is under-treated” but differs “from true addiction because such behaviors can be resolved with effective pain management.” *Resources for Pain Management: Understanding Tolerance, Physical Dependence and Addiction*, Let’s Talk Pain, https://web.archive.org/web/20120322234928/http://www.letstalkpain.org/real_story/addictions.html.

- Janssen's *Prescribe Responsibly* website states that addiction might be "pseudoaddiction," defined as "a syndrome that causes patients to seek additional medications due to inadequate pharmacotherapy being prescribed," and "[t]ypically when the pain is treated appropriately, the inappropriate behavior ceases." Keith Candiotti, M.D., *Use of Opioid Analgesics in Pain Management, Prescribe Responsibly*, <http://www.prescriberesponsibly.com/articles/opioid-pain-management>.

Comment: As detailed in the Report, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept. Further, by introducing the concept of pseudo-addiction, Defendants made it more difficult for prescribers to detect and treat prescription opioid addiction, encouraged prescribers to increase opioid doses, and thereby further endangered those patients who became addicted to the opioids received through the health care system.

Appendix I.D: Endo Pharmaceuticals**Endo Misleading Messaging****A. Benefits of Opioids Overstated****1. Myth: Opioids are effective for chronic pain**

- “[P]ain leaders recognize the need... to arrive at a unified agenda and establish a framework that supports better understanding of this therapy and the benefits and risks of prescribing opioid medication. While the pain community must call attention to the epidemic of **chronic pain**, its undertreatment, and the **utility of opioid therapy as a safe and effective** strategy to relieve pain and improve functioning in appropriately selected and monitored patients, it also must acknowledge the societal and public health concerns raised by reports of increasing prescription drug abuse.” “Provider Prescribing Patterns and Perceptions: Identifying Solutions to Build Consensus on Opioid Use in Pain Management—A Roundtable Discussion,” American Pain Foundation. Published April 2008. (emphasis added). The Report states that it was “supported by an educational grant from Endo Pharmaceuticals.” ENDO-OPIOID_MDL-02212377 at 2380-2381.
- “Pain affects more Americans than diabetes, heart disease and cancer combined. Now is the time to build consensus on pain management **on opioid use** in America and drive perceptions towards a more balanced view. Alleviating pain in patients with legitimate medical needs remains an important medical imperative. Patients deserve optimal pain relief, which includes access to **safe and effective** pain medications balanced with appropriate risk management. When properly prescribed by a healthcare professional and taken as directed, these medications provide **important pain relief and can improve functioning.**” *Id.* at 2381(emphasis added).
- “A key challenge is the **lack of scientific studies that have evaluated long-term safety and efficacy** of opioids for non-cancer pain.” *Id.* at 2380 (emphasis added).
- “The **absence of controlled clinical trials evidence must not be misinterpreted to be ‘lack of evidence.’** As defined by the principles of evidence-based medicine, the cumulative experience of myriad

practitioners and their patients presents a robust body of evidence; however, the need for better science in this area is abundantly clear.” *Id.* at 2387 (emphasis added).

Comment: These quotes exemplify the Industry’s misleading promotional messages, which perpetuated the unsupported claim that opioids are ‘safe and effective’ for ‘chronic pain,’ and minimized the importance of controlled trials showing safety and efficacy beyond 16 weeks. As to the claim of efficacy of opioids for chronic pain, there was not then, and there has never been, reliable evidence to support the claim. The Endo-sponsored report tries to have it both ways. While acknowledging the lack of “scientific studies that have evaluated long-term safety and efficacy,” the Report asserts that “cumulative experience” constitutes “robust evidence” under principles of evidence-based medicine. That is not correct. “Cumulative experience” is anecdotal and does not qualify as evidence-based medicine. While experience may *complement* scientific studies, experience is not a *substitute* for such studies, especially in the face of mounting evidence of harms. Further, a gold standard one-year randomized clinical trial (Krebs, 2018) demonstrated that opioids are not superior to non-opioid therapy for patients with chronic pain. This result refutes 20 years of the Industry’s reliance on anecdotal, non-scientific studies to claim that long-term opioid therapy is “safe and effective.”

Comment: The American Pain Foundation (APF), which published the 2008 Report, dissolved in 2012 due to irreparable economic circumstances after a ProPublica/Washington Post article “detailed its close ties to drugmakers.” The article found that APF’s “guides for patients, journalists and policymakers had played down the risks associated with opioid painkillers while exaggerating the benefits.” See Charles Ornstein, *et al.*, *American Pain Foundation Shuts Down as Senators Launch Investigation of Prescription Narcotics*, ProPublica (May 8, 2012) <https://www.propublica.org/article/senate-panel-investigates-drug-company-ties-to-pain-groups>.

2. ***Myth: Opioids are effective for long-term use based on short-term studies***

- “Opana ER’s 12 hour dosing has been proven in many patient types including opioid-naïve patients with low back pain. In a clinical trial with opioid-naïve patients, 81% of patients on OPANA ER had a >= 30% pain score reduction compared with only 52% of patients on placebo. Even

more impressive, greater than 70% of these patients achieved a $\geq 50\%$ pain score reduction.” Endo OPANA ER Call Plan Document Message and Support Materials, February 2007. ENDO-CHI_LIT-00210473 at 0475.

Comment: This quote, created for its sales representatives, was a reference to an article by Katz *et al.* which was biased and misleading, and included Endo employees as authors and was Endo sponsored. The claim that over 70% of patients on oxymorphone extended release (Opana ER) achieved greater than 50% pain relief was misleading because the “ $>70\%$ ” figure, who purportedly achieved $> 50\%$ pain reduction, was based on only the fraction of patients randomized to Opana who were able to complete the randomized controlled trial. In reality, 325 patients were recruited for the open label “enriched enrollment” phase which exposed all 325 to Opana. 120 discontinued before the randomized controlled trial (RCT) even began. So only 63% (205/325) could tolerate Opana at all, let alone achieve $>50\%$ pain relief. Furthermore, following the initial enriched enrollment phase, another 33% of the subjects randomized to Opana also failed to complete the trial due to adverse effects or lack of efficacy. By ignoring the substantial percentage of patients who could not tolerate Opana at all (37%), and those who subsequently dropped out of the drug arm of the trial (33%), Endo trained its sales team to mislead physicians about its efficacy by making the false claim that “over 70%” achieved over 50% pain relief. Further, although the Katz article did not explicitly state that Opana can be used long-term for chronic pain, the training does not instruct the salesforce to limit use to 12 weeks. (ENDO-CHI_LIT-00210473 at 0474) Also note that the Hale study, to be used for the same sales calls, explicitly stated in the abstract that Opana provides “long-term analgesia,” despite a study length of only 12 weeks. The claim of “long-term analgesia” is misleading in the context of a 12-week study.

3. ***Myth: Opioids are first-line treatment***

- Listed under benefits of Opana ER - “Proven first line therapy for opioid-naïve patients.” Endo OPANA ER Call Plan Document Message and Support Materials, February 2007. ENDO-CHI_LIT-00210473 at 0475.

Comment: By not distinguishing between acute pain and chronic pain, this quote sends the misleading message that using Opana ER for chronic pain is evidence-based. While there is reliable evidence of efficacy of

opioids for acute pain, as noted above and in the Report, there is no reliable evidence of efficacy for chronic, non-cancer pain.

B. Risks of Opioids Understated

1. *Myth: Opioid Therapy is “Safe”*

- Comment: As to the assertion in the 2008 APF Report that opioid therapy is “safe” in “appropriately selected and monitored patients,” (see above): There were numerous studies that had reported a range of addiction as high as 24% before the opioid sellers began increased, widespread sale and distribution of opioids, without any reference to those data, and numerous additional, subsequent studies consistent with the earlier results. There was no reliable basis to assert that addictive drugs were not addictive simply because they had been prescribed by a doctor. As noted in the Volkow/McClellan article cited in the Report, “no patient is immune from addiction.” Regarding “appropriately selected and monitored patients,” as detailed in the Report, we do not have any reliable tools or screening instruments to predict who will get addicted to opioids prescribed in the course of medical treatment.

2. *Myth: Opioid dependence is not a significant problem and no different from other drugs*

- “Physical dependence and tolerance are related phenomena that occur with chronic use of many types of drugs, including many that are not associated with addiction or abuse (such as beta blockers for high blood pressure). Both result from changes in the body as it adapts to the constant presence of the drug. Physical dependence is due to adaptive changes that cause the body to depend on the drug’s actions to drive a process.” Oxymorphone Learning System, Module 3, Oxymorphone Risk Management Program (For Sales Training Background Purpose Only), 2006. ENDO-CHI_LIT-00053284 at 3299.

Comment: This statement is misleading because withdrawal from “beta blockers for high blood pressure” cannot compare to withdrawal from opioids, which is so painful that it can lead to suicide, death due to autonomic instability, and pursuit of illicit sources of opioids.

3. Myth: Pseudo-addiction – respond with more opioids

- The Learning System manual noted that “[t]he physician can differentiate addiction from pseudoaddiction by speaking to the patient about his/her pain and increasing the patient’s opioid dose to increase pain relief.” *Id.* at 3299.
- “Pseudoaddictive behaviors such as clock watching (counting down the time until the next dose) will resolve when the pain is properly treated.” *Id.* at 3299.
- “The syndrome of drug-seeking behaviors that arises when a patient cannot obtain adequate relief with the prescribed dose of analgesic and seeks alternate sources or increased doses of analgesic is referred to as pseudoaddiction. This may be the result of increasing pain due to disease progression, development of a new condition, or inadequate instruction or dose provision by the clinician.” Opioid Analgesics for Pain Management: Critical Thinking to Balance Benefits & Risk [Endo had financial relationships with 5/5 faculty for this CME] June 2007, expires June 2009. CHI_001222272 at 2279

Comment: As detailed in the Report, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept. “Speaking to the patient” is particularly misleading advice, since numerous studies have documented the false statements provided by patients to their doctors in order to maintain access to addictive opioids.

4. Myth: Abuse deterrent formulations decrease risk of addiction

- “Options . . . 1. The next generation of Opana ER was formulated using the INTAC™ technology which is designed to discourage misuse and abuse of the medication. 2. The next generation Opana ER was formulated to reduce the likelihood of abuse and misuse. 3. The FDA-approved formulation of Opana ER was developed with tamper-resistant properties to discourage abuse and misuse. 4. With a formulation that is designed to be crush-resistant, Opana ER represents the next generation of pain

management medications. 5. The reformulated tablet is designed to make it more difficult for Opana ER to be split, chewed, crushed, or dissolved to release the medication more rapidly than intended.” Draft Communication Messages for Opana ER, November 17, 2011. END00099670 at 9670-9671.

- “A study of prescription opioid abusers in a drug rehabilitation program found that 80% tampered with opioid tablets to accelerate drug release by chewing or administering the drug intra-nasally or intravenously. The authors suggest that formulations that incorporate physical or pharmacologic impediments to altering the recommended routes of administration may deter tampering; The attractiveness of an opioid for abuse is in large part dependent on characteristics of the tablet formulation particularly the ease with which it can be crushed or dissolved in fluids.” Letter requesting support from Julie Suko Regarding: Reformulated Opana ER (oxymorphone hydrochloride) Extended-Release Tablets, CII with INTAC® technology (Designed to be crush resistant), November 6, 2012. ENDO-OR-CID-00772464 at 2464.

Comment: Opana ER was at the center of the injection opioid epidemic in Scotts County, Indiana in 2015 that led to the spread of HIV in that community. “From November 18, 2014 to November 1, 2015, HIV infection was diagnosed in 181 case patients. Most of these patients (87.8%) reported having injected the extended-release formulation of the prescription opioid oxymorphone...Persons who reported injecting oxymorphone frequently described crushing, dissolving and cooking extended-release oxymorphone (Opana ER, Endo Pharmaceuticals).”⁶⁴⁰ In other words, “abuse via injection” was not more difficult. The most common way that people misuse and get addicted to prescription opioids, is to ingest oral formulations orally as prescribed. Although tamper-resistant formulations may make it more difficult to crush, snort, or inject these substances, that is no protection against getting addicted to them in the first place, taken as prescribed. Further, as with Opana ER, which was supposed to be tamper resistant, addicted persons were able to crush and inject it.

⁶⁴⁰ See Peters, et.al., “HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014-2015” *N Engl J Med* 2016;375:229-39, at pp. 229 and 232.

5. Myth: Addiction/abuse is rare/low

- “What is the risk of becoming addicted to a long-acting opioid?” “Most healthcare providers who treat patients with pain agree that patients treated with prolonged opioid medicines usually do not become addicted.” 2009 Opana ER “Instant Savings” card ad Resource Kit promising up to \$300 in savings. 2009 Opana ER “Instant Savings” card and Resource Kit, ENDO-CHI_LIT-00541205 at 1211.
- “Most doctors who treat patients with pain agree that patients treated with prolonged opioid medicines usually do not become addicted.” Endo’s website for Opana, www.Opana.com (until at least 2012). END00474717 at 4739.

Comment: These comments are misleading because they suggest addiction is rare in patients treated with opioids. Addiction risk with opioid therapy is common, not rare.

6. Myth: No dose is too high

- “Some people taking opioids may need to take a higher dose after a period of time in order to have relief from their pain. This is ‘tolerance’ to opioids medications that doesn’t affect everyone who takes them and does **NOT** mean addiction. (Emphasis in original). If tolerance develops, it does not mean you will ‘run out’ of pain relief. Your healthcare provider can adjust your dose or prescribe another medicine.” 2009 Opana ER “Instant Savings” card and Resource Kit, ENDO-CHI_LIT-00541205 at 1211.
- “[W]hat should I know about opioids and addiction?” “If tolerance does occur, it does not mean you will ‘run out of’ pain relief. Your dose can be adjusted or another medicine can be prescribed.” Understanding Your Pain: Taking Oral Opioid Analgesics brochure. ENDO-CHI_LIT-00237187 at 7189.

Comment: In fact, tolerance is a good indicator that the patient will ‘run out’ of pain relief. Tolerance indicates neuroadaptation to the opioid molecule, and the need for higher doses to get to same effect and/or stave off withdrawal. Since higher doses are associated with more morbidity and

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mortality, increasing doses of opioids are dangerous. These statements perpetuate the misleading claim that tolerance is a benign condition that is not associated with addiction.

Appendix I.E: Allergan**Allergan Misleading Messaging****A. Benefits of Opioids Overstated****1. Myth: Opioids are effective for chronic pain**

- “Longer-acting agents are more effective than short-acting agents for chronic pain; “around-the-clock” dosing for “around-the-clock pain”. Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009. ALLERGAN_MDL_01741588 at 1596.

Comment: This quote exemplifies the claim that opioids are effective for chronic pain, which was not then, and has never been, supported by reliable evidence.

- “Morphine and morphine-like drugs work well for pain and are safe when taken as directed by a doctor.” *Id.* at 6826.

Comment: As detailed in the Report, there is not now and has never been reliable evidence that opioids are effective for long-term treatment of chronic pain.

2. Myth: Opioids are first-line treatment

- “How does Kadian fit into your prescribing habits? If first line...Thank the HCP for their business and remind them of the key features and benefits of Kadian. If not first line: Why don’t you use Kadian first line?” Kadian Marketing Overview - Sales Representative Training, October 2011. ALLERGAN_MDL_00007268 at 7294. Same presentation used in February 2013, *see* ALLERGAN_MDL_00026506 at 6533.

Comment: The quote above does not distinguish between acute pain and chronic pain. The implied “key feature” of Kadian is its longer duration of action for “around the clock” pain, *i.e.* chronic pain. While there was reliable evidence of efficacy of opioids for acute pain, as noted above and in the Report, there was no reliable evidence of efficacy for chronic, non-cancer pain. It was misleading to make a blanket statement of efficacy without making this distinction clear.

3. Myth: Opioids are safer than the alternatives

- “Maintenance therapy with opioids can be safer than the long-term use of other analgesics, such as COX-2 inhibitors, nonselective NSAIDs, or acetaminophen . . .” Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009.
ALLERGAN_MDL_01741588 at 1598.

Comment: There was no reliable evidence to claim that opioids were “safer, or “perhaps” safer than NSAIDs or acetaminophen. As to NSAIDs, the best available evidence shows that opioids confer greater risk of mortality and adverse events. (*See* Solomon study in the Report); also, the Krebs study (SPACE trial) in the Report, found more adverse events in the opioid group than among the non-opioid group that consisted of acetaminophen and NSAIDs, with a small percentage of patients on tramadol.

4. Myth: Opioids improve function/quality of life

- “Proven efficacy and improvement in quality-of-life (QOL) sleep scores in patients with chronic back pain.” Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009.
ALLERGAN_MDL_01741588 at 1632.
- “. . . Many Americans suffer from chronic or ongoing pain. It can cause you to miss work and can even keep you from enjoying life. If left untreated, pain can place stress on your body and your mental health” and “Chronic pain . . . can be inconvenient and can keep you from your daily tasks.” The FDA objected to these statements in prior brochures. Letter to FDA from Actavis, July 16, 2010. ALLERGAN_MDL_01237743 at 7750.

Comment: The above quotes imply that opioids will improve function and mental health, when the data show little or no improvement in function with opioid therapy, and more adverse medical events. Indeed the high drop outs rates in many opioid studies, even short term, suggest that many people do not tolerate opioids. Also, studies have linked the use of opioids with depression and suicidality, not improvements in mental health. Burgeoning evidence shows significant morbidity and mortality with opioids, increasing with dose and duration.

B. Risks of Opioids Understated

1. *Myth: Addiction is rare*

- “Opioids can be used with minimal risk in chronic pain patients without a history of abuse or addiction.” Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009.
ALLERGAN_MDL_01741588 at 1596.

Comment: Opioids cannot be used for chronic pain without imposing significant risks of addiction, dependence, withdrawal and multiple adverse effects. It is misleading to claim that risks were “minimal.”

2. *Myth: The problem is the ‘addicts,’ not the drug*

- “However, despite the continued unscientific beliefs of some clinicians, there is no evidence that simply taking opioids for a period of time will cause substance abuse or addiction. It appears likely that most substance-abusing patients in pain management practices had an abuse problem before entering practice.” Kadian Learning System.
ALLERGAN_MDL_01052119 at 2254.

Comment: This quote perpetuates the misleading idea that the problem is the addicted patient, not the inherently addictive nature of the opioid. In fact persons with no personal or family history of addiction can become dependent on, addicted to, and die from opioids through a medical prescription.

3. *Myth: Tolerance - Respond with higher dose*

- “Upward titration of pure opioid agonists can theoretically be continued indefinitely, because there is no absolute ceiling effect to these medications. In practice, however, although this is sometimes performed in cases of cancer pain, most physicians will try an alternative medication once they have exceeded their own comfort level with a given drug.”
Kadian Learning System. ALLERGAN_MDL_01052119 at 2221.
- “Pseudotolerance—Pseudotolerance is the need for an increase in dosage that is not due to tolerance, but is due to other factors, such as disease

progression, new disease, increased physical activity, lack of compliance, change in medication, drug interaction, addiction, and deviant behavior.” Kadian Learning System. ALLERGAN_MDL_01052119 at 2305.

Comment: The statements above are misleading because they omit that increased dose increases risk of dependence, addiction, and numerous adverse effects, including death. “Pseudotolerance” is not a recognized diagnosis, whereas “tolerance” is almost universally the reason why opioid users seek increased dosage of the drugs.

4. *Myth: Pseudo-addiction – respond with more opioids*

- “The problem is even more complex because some patients who are undertreated for their physical pain show the symptoms of “pseudoaddiction.” Pseudoaddiction is a set of behaviors . . .that are exhibited by patients with inadequately treated pain, including patients with cancer pain. Pseudoaddictive behaviors are not signs of substance abuse, but rather should be considered symptoms of inadequate treatment.” Kadian Learning System. ALLERGAN_MDL_01052119 at 2150.
- “Pseudoaddiction—Pseudoaddiction is drug-seeking behavior that seems similar to addiction but is due to unrelieved pain. This behavior stops once the pain is relieved, often through an increase in opioid dose.” Kadian Learning System. ALLERGAN_MDL_01052119 at 2305.

Comment: As detailed in the Report, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at an opioid seller, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept.

5. *Myth: Opioid dependence is easily reversible*

- “Development of Tolerance and Physical Dependence is a major reason some clinicians feel opioid therapy should be limited for patients with CBP. Most clinicians do not consider this a major issue, however. Although tolerance and dependence do occur with long-term use of opioids, many studies have shown that tolerance is limited in most patients with CBP. Physical dependence simply requires a tapered withdrawal

should the opioid medication no longer be needed.” Kadian Learning System (Altier Ex. 2 / ALLERGAN_MDL_01610522 at 0848).

Comment: Dependence and tolerance are serious physical conditions in themselves, leading to increased doses and addiction in a subset of patients, and to long, slow, and often failed attempts at tapering. Abrupt discontinuation or rapid tapering of opioids can cause extreme suffering in the majority of patients on chronic opioid therapy, and may even lead some to experience suicidal thoughts and/or turn to illicit sources of opioids.

Anna Lembke, M.D. Report

APPENDIX II

Summary of Documents from the University of Wisconsin
Pain and Policy Study Group (PPSG)

Appendix II: Documents from the University of Wisconsin Pain and Policy Study Group

1. Documents produced by the University of Wisconsin Pain and Policy Studies Group (PPSG) in this case are supportive of Dr. Joel Saper's statements concerning the relationship between "narcopharma," as he referred to the Industry, and David Joranson, who was Director of the PPSG. (*See Report at section C.4.g.*) These documents provide evidence that the Industry funded PPSG over a period of many years, and that PPSG, in turn, carried out programs that benefitted the Industry by increasing access to opioids and limiting regulatory scrutiny of prescribing doctors.

2. On September 9, 1996, John Stewart wrote an email to Robert Kaiko of Purdue Pharma, recounting a discussion with David Joranson and Sophie Colleau at a pain conference in Vancouver, and Dr. Colleau's follow-up letter that included a reference to a UN report concluding that "the medical need for opioids is far from being met, and recommend[ing] specific steps that should be taken by governments, non-governmental organizations and health professionals- to increase the availability and use of opioids." Stewart informs Kaiko that "In the past, we have provided modest financial support for the Wisconsin Pain Research Group (in the form of annual corporate membership) and would be inclined to provide same (\$1,000 to \$2,000) toward this activity." Kaiko wrote back "They are seeking support that will not only cover this, but also, subsequent issues of the publication. To date I believe they are planning for 5k from Janssen and from Purdue 4k (2k in basic support and 2k for ?# copies in Spanish for our use in Latin America.)" PPLPC013000017513.

3. On December 20, 1996, PPSG Director Joranson and several others wrote a letter to "Dear Colleague," to inform about "the new Pain & Policy Studies Group (PPSG)," following the departure of the former head of the Pain Research Group to a new position. The letter advised that, "In the US, our group will continue its work to identify and address regulatory barriers to pain management We will expand our work with cancer and palliative care organizations and governments in a number of countries in order to achieve more balanced opioid regulation and improved availability of opioid analgesics." PDD1701481531. The stated goals of PPSG thus included making opioids more available for treatment of pain, an objective that matched well to those of the sellers of such drugs.

4. On October 5, 2000, Director Joranson sent an email to David Haddox and Robert Kaiko of Purdue Pharma, enclosing four items that Joranson had been working on, including a document titled, "Evaluating federal and state policy for balance," which had also been sent to Dr. Sackler. Dr. Joranson's email closed with, "Hope to have a cocktail or something with you in not too long!" Haddox replied, "I think it is an excellent work product." WIS_PPSG_001791. As noted throughout the PPSG documents, the principle of "balance" asserts that efforts to control diversion and abuse should not interfere with access to prescription opioids for pain; this principle was central to the Pharmaceutical Opioid Industry's ability to achieve widespread opioid use.

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5. On August 30, 2001, Joranson wrote to Chris Neumann, Senior Director of Medical Education at Purdue Pharma, to acknowledge receipt of a \$75,000 grant to “help us maintain our program and accomplish our pain and policy goals.” WIS_PPSG_013938.

6. On September 9, 2002, Joranson wrote to Robert Kaiko of Purdue, regarding “the points I would make about the value of our work: … 2. “We have improved state medical board policies: … Many states now have improved pain/opioid policies that address concerns about regulatory scrutiny; we developed much of it from behind the scenes, we wrote the two models that states have used, the medical board guidelines from CA and the model guidelines of the federation of state medical boards… 4. Evaluation of state policies for impediments to the use of opioids for pain.” WIS_PPSG_006938

7. On October 9, 2002, Joranson again wrote to Mr. Kaiko, expressing appreciation for support provided by Purdue “for the past several years. Without your support, some of the progress reported below would not have been possible.” Joranson then asked for an additional grant of \$175,000 for this year, renewable for two more years. WIS_PPSG_006457.

8. On February 21, 2005, PPSG Director Joranson/PPSG gave a presentation to the American Pain Society, entitled, “Pain Policy in the U.S.: Are We Moving Forward?” The presentation included slides providing results of 3 national surveys of medical board members, in 1991, 1997, and 2004, under the heading “Education and research with medical regulators.” The next slide stated that “Prescribing an opioid analgesic for more than several months to treat a patient with Chronic non-cancer pain was “Lawful/generally accepted medical practice for 12% (1991), 33% (1997) and 67% (2004) of surveyed medical boards.” WIS_PPSG_000703, produced natively at *6. PPSG’s Industry-funded efforts to remove prescribing restrictions significantly contributed to this drastic change in the acceptability of opioid treatment of chronic non-cancer pain.

9. Joranson’s 2005 presentation continued with a description of PPSG’s Model Policy Development, in particular, the FSMB Model Guidelines (1998) and FSMB Model Policy (2004), adopted in full by 13 states and in part by 12 states. The Model Policy advanced by PPSG “Recognizes need for opioids;” “Pain relief part of quality medical practice;” “Should not fear investigation;” and that “Inappropriate tx [treatment] includes over, under, non-treatment, continued ineffective tx.” (*Id.* at *8-*10). The designation of “undertreatment” of pain as “inappropriate” was a common theme in the promotion of opioids as the solution. The question of undertreatment of pain and the scope of the population arguably affected vary widely according to how the terms are defined. Regardless, the use of long-term opioid therapy is not and has never been the solution to chronic non-cancer pain.

10. Joranson’ presentation included a slide on “The Principle of Balance,” which stated, “Central to protecting public health and safety: Opioids are safe and effective, necessary,”

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and that “Opioids have potential for abuse, pose risks.” (*Id.* at *16). Reliable scientific evidence demonstrates that opioids are dangerous and deadly, not “safe;” no reliable scientific evidence demonstrated that opioids were effective for the treatment of chronic non-cancer pain. Joranson’s industry-funded presentation was misleading.

11. Another of Joranson’s February 2005 presentation slides listed “16 States Improved Pain Policies (2000-2003), including West Virginia among them. “Examples of Policy Changes” included “Encourage pain management, pain management part of quality professional practice, address fear of regulatory scrutiny.” (*Id.* at *18-*19). Eight slides are devoted to the topics of diversion and abuse (*Id.* at pp. *23-*30). The presentation stated, “The reasons for increased abuse should be studied, taking into consideration all the sources of abused opioids, including deliberate criminal activities to divert opioids from all levels of the distribution system. Source and amount matter. Meanwhile, we should ensure that efforts to address abuse and diversion do not interfere in pain management.” (*Id.* at *31). No slides in the presentation are devoted to risk of addiction or the powerful addictive properties of prescription opioids, including the risk to individuals who are receiving opioids as medical treatment, and not only to “abusers.”

12. On June 6, 2005, PPSG Director David Joranson and Assistant Director Aaron Gilson wrote to Robert Kaiko, VP of Clinical Research at Purdue and Pamela Bennett, Purdue, Director of Advocacy, to express appreciation for “the last three years of financial support that Purdue Pharma has provided to [PPSG], amounting to \$100,000 annually for the US program and \$175,000 annually for the international program.” This amounts to \$825,000 of financial support to PPSG from Purdue alone, in that 3-year period. The letter summarized PPSG’s “recent achievements” and requested an additional \$2.2 million from Purdue for the years 2006-2010. The first listed “achievement was as follows: “In the USA, between 2000 and 2003, 16 States took legislative and regulatory actions to improve their pain policies. Many of these actions were based on our evaluations, recommendations and technical assistance and were accomplished in collaboration with many governmental and nongovernmental groups which use PPSG policy evaluations as a road map.” WIS_PPSG_008286.

13. In an August 2005 email thread referencing the enactment of the “North Dakota Pain Bill,” an email was sent to Aaron Gilson, Assistant Director of PPSG, asking: “Did you guys have a hand in this one? This is certainly what I’ve espoused for years, since we realized intractable pain acts weren’t really that helpful—that all we needed in statute was a statement that practitioners could legally prescribe opioids for pain.” WIS_PPSG_000026; WIS_PPSG_000036. Gilson responded, “I’m impressed that you could detect our finger prints . . . I’ll wear gloves next time. Yes, we worked with Bruce Levi, Executive Director of the North Dakota Medical Association, to change ND’s IPTA[Intractable Pain Treatment Act] to a general pain statute, which also removed the prescribing restriction for ‘addicts.’” WIS_PPSG_000026;

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WIS_PPSG_000036. This exchange is indicative of not only the type of PPSG projects that benefited the Industry by easing prescribing restrictions and penalties, but also shows the surreptitious, behind-the-scenes nature of PPSG's efforts.

14. In a November 2005 "Prospectus," PPSG listed a number of policies and programs to attract financial support. The Prospectus described PPSG's promotion of "the principle of 'balance' which recognizes that policies aimed at preventing drug abuse must not interfere with medical practice and patient care." To promote that policy, PPSG published "State Profiles that identify provisions in each state that have the potential to enhance or impede pain management. ... PPSG assigns grades to each state to draw attention to the need to improve pain policy. ... A Progress Report Card compared the policies in 2003 with those in 2000 and found that many states had improved the degree of balance in their pain and regulatory policies. PPSG identifies and recommends 'best' or model policies and assists in their development." WIS_PPSG_008292 at pp. 2-3. The "Accomplishments" section of the Prospectus stated, "PPSG played a central role in revising the Federation of State Medical Board's Model Guidelines on the Use of Controlled Substances for Pain Management, now entitled Model Policy for the Use of Controlled Substances for Pain Management." (*Id.* at p. 4). The FSMB Model Guidelines played a significant role in exacerbating the prescription opioid epidemic, by eliminating or reducing restrictions on use of opioids for pain, and by threatening regulatory action for "undertreated pain."

15. PPSG also worked with the FSMB to develop and present an educational program for "workshops for state medical board members held across the U.S.; PPSG staff served as faculty, and administered a pre- and post-test survey to evaluate changes in knowledge and attitudes as a result of workshop participation." WIS_PPSG_008292, 11/30/2005.

16. On December 1, 2005, Joranson and Gilson of PPSG wrote to Bobbie Sue Brown, Clinical Development & Education Manager-Southwest, at Endo Pharmaceuticals, recounting the work of PPSG and requesting \$225,000 for the period 2006-2008. WIS_PPSG_007994.

17. A document titled, "U.S. Program Accomplishments: July 2009-June 2010," stated: "PPSG remains a member of the Federation of State Medical Boards Research and Education Foundation's advisory committee that recently developed a handbook to educate physicians about the Federation's Model Policy to promote safe and effective prescribing and reduce the risk of abuse, addiction, and diversion of opioids and other controlled substances in office-based pain management; the Handbook was published mid-2007 and is being made available to state medical boards to distribute to their licensees. [Fishman SM. Responsible opioid prescribing: A physician's guide. Washington, DC: Waterford Life Sciences; 2007.]" WIS_PPSG_007680, 02/07/2011, at p. 3.

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18. The 2007 Fishman Handbook encouraged use of prescription opioids for chronic pain, despite absence of reliable evidence of long-term efficacy. Dr. Fishman's disclosure for a Continuing Medical Education (CME) program based on the Handbook listed Endo, Janssen and Cephalon among his financial supporters. https://archive.org/stream/279187-responsible-opioid-prescribing-info/279187-responsible-opioid-prescribing-info_djvu.txt. The CME website listed the consortium members who supported publication of the Handbook, including Purdue Pharma, Endo, Cephalon, Alpharma, and the PPSG; the CME target audience was described as "Physicians who prescribe opioid analgesics as part of pain management strategies in their clinical practice." (*Id.*) In short, PPSG cooperated with the Pharmaceutical Opioids Industry to produce a Handbook funded by the Industry to promote its views of "responsible prescribing;" that book was then used to "educate" physicians for CME credit, to be earned by reading the book and passing an online test on its contents.

19. The "U.S. Program Accomplishments: July 2009-June 2010" document also included the following entry: "PPSG published a review article describing the implications of inaccurate addiction-related terminology, contained in current federal and state laws, regulations, and guidelines/policy statements, on effective pain management and patient care; data used to inform sections of this manuscript was obtained through a recently-completed grant to examine the legislative and regulatory origins of restrictive policy language that currently is present in state law and has a potential to interfere with the adequate and effective use of controlled substances for pain management. [Gilson AM. The concept of addiction in law and regulatory policy: A critical review. Clinical Journal of Pain. 2010; 26(1):70-77.]" WIS_PPSG_007680 (emphasis added). Removing restrictions and interference with opioid prescribing were the stated goals of PPSG and aligned with its Industry funders.

20. A PPSG Spreadsheet lists financial contributions from the Pharmaceutical Opioid Industry between November 2000 and August 2007, including: Purdue Pharma, \$1,256,500; Janssen/J & J: \$238,990; Endo, \$140,000; Ortho-McNeil, \$125,000; Cephalon, \$25,000; Alpharma, \$25,000; Roxane, \$15,000; and Abbott, \$15,000 for a total of \$1,840,490. The spreadsheet lists 27 separate contributions by Purdue, and 10 each by Janssen/J&J and Endo; the frequency and collegial nature of the communications between PPSG and company representatives like David Haddox suggests a cooperative relationship. Additional payments occurred outside of the years covered by the spreadsheet. WIS_PPSG_007783.

21. A presentation by Joranson on February 16, 2008 disclosed financial relationships with Abbott, Alpharma, Cephalon, Endo, Ortho-McNeil, and Purdue Pharma. WIS_PPSG_007991. However, Joranson's presentation slides did not include such disclosures in February 2005. WIS_PPSG_000703.

22. A 2011 spreadsheet lists the following contributions as “Pending”: Actavis, “to be \$55k;” Allergan \$50,000; Endo, \$46,106; \$649,779; \$46,057; and \$75,000; Janssen Ortho Pricara, \$50,000; and \$10,000; and Purdue, \$50,000. WIS_PPSG_003892.

23. These documents provide supportive evidence for my opinion that one of the ways that the Pharmaceutical Opioid Industry created the opioid epidemic in the United States was by funding the PPSG to “educate” the medical community as to the “necessity” for such drugs, to influence state legislatures to increase access while loosening restrictions on prescribing, and to change the very culture of opioid prescribing, by suggesting that failing to prescribe opioids was tantamount to “undertreating” pain and violating a patient’s “rights.”

Anna Lembke, M.D. Report

APPENDIX III

Case Specific Data: *Cabell County Commission and City of Huntington, West Virginia, (The Cabell Huntington Community) v. AmerisourceBergen Drug Corporation, Cardinal Health, Inc., and McKesson Corporation*

Appendix III: Case specific data and information

A. Background of the Case:

1. It is my understanding that the plaintiffs in this action are the Cabell County Commission and the City of Huntington, West Virginia.
2. It is my understanding that the defendants in this action are as follows: AmerisourceBergen Drug Corporation, Cardinal Health, Inc., and McKesson Corporation.
3. It is my understanding that the claim of relief in this litigation is Public Nuisance, as described in the Complaint: 1) Defendants created and maintained a public nuisance which proximately caused injury to Plaintiff; 2) Defendants repeatedly engaged in unlawful and wrongful conduct which reasonably interfered with and had a substantial impact upon the public health, giving rise to the opioid epidemic; 3) A public nuisance results from conduct that caused an unreasonable and substantial interference with a right common to the general public, which is the proximate cause of, and/or substantial factor leading to, Plaintiffs' injury. 4) Defendants have created and maintained a public nuisance by marketing, distributing, selling opioids, and/or exacerbating the flood of opioids into Plaintiff's Community in ways that unreasonably interfere with the public health, welfare, and safety in Plaintiffs' Community. Plaintiffs and residents of Plaintiffs' Community have a common right to be free of such conduct and to be free from conduct that creates a disturbance and reasonable apprehension of danger to person and property.

B. Opioid Prescribing:

1. As shown in the Tables below, between 2006-2014, West Virginia's average annual dosage unit per capita for oxycodone and hydrocodone was significantly greater than the national annual dosage unit per capita for oxycodone and hydrocodone.⁶⁴¹
 - a. The Average Annual Dosage Unit per capita for 2006-2014 in West Virginia amounted to 72.05 compared to 39.90 for the nation.⁶⁴² Within West Virginia, Cabell County and the City of Huntington had a substantially higher average level of 122.08 Total Dosage Units per year.⁶⁴³ The average for Cabell/Huntington was approximately 3 times greater than the national average.

⁶⁴¹ Report of Craig McCann, Appendix 10 at pp.75,90

⁶⁴² *Id.*

⁶⁴³ *Id.*at p. 106

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West Virginia Opioid Shipments by Buyer Business Activity, in Dosage Unit														
Buyer Business Activity	# of Customers	# of Transactions	Total Dosage Unit	Annual Dosage Unit Per Cap	2006	2007	2008	2009	2010	2011	2012	2013	2014	
...	
Grand Total	1,841	2,745,325	1,197,161,809	100.0%	72.05	106,893,252	123,117,844	136,778,544	141,771,908	137,380,756	143,355,564	142,280,807	134,938,947	130,644,187

National Opioid Shipments by Buyer Business Activity, in Dosage Unit														
Buyer Business Activity	# of Customers	# of Transactions	Total Dosage Unit	Annual Dosage Unit Per Cap	2006	2007	2008	2009	2010	2011	2012	2013	2014	
...	
Grand Total	221,914	271,719,367	110,942,115,712	100.0%	39.90	9,500,006,222	10,634,154,340	11,504,423,367	12,363,113,878	13,104,935,866	13,930,744,757	13,823,896,352	13,266,351,152	12,814,436,749

Cabell County and the City of Huntington, WV Opioid Shipments by Buyer Business Activity, in Dosage Unit														
Buyer Business Activity	# of Customers	# of Transactions	Total Dosage Unit	Annual Dosage Unit Per Cap	2006	2007	2008	2009	2010	2011	2012	2013	2014	
...	
Grand Total	144	208,024	109,811,500	100.0%	122.08	11,113,188	12,585,604	13,733,708	13,547,322	12,706,490	12,626,278	11,550,800	10,579,934	11,368,176

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- b. Morphine Milligrams Equivalent (MME) is a standard measure of the strength (and magnitude of risk) of opioids. As shown by the Tables below, average annual MME for Cabell County and the City of Huntington was 1,168.81, which was significantly higher than the average for West Virginia (642.75), which, in turn, was significantly greater than the average for the US (384.51). As is true for annual dosage units per capita (above) the average annual MME per capita for Cabell County/City of Huntington was also approximately 3 times greater than for the US generally, increasing annual MME per capita of 642.75 for the period from 2006-2014.⁶⁴⁴

West Virginia Opioid Shipments by Buyer Business Activity, in MME														
Buyer Business Activity	# of Customers	# of Transactions	Total MME	Annual MME Per Cap	2006	2007	2008	2009	2010	2011	2012	2013	2014	
...	
Grand Total	1,841	2,745,325	10,679,095,523	100.0%	642.75	556,359,903	977,668,231	1,120,018,778	1,213,465,584	1,227,124,068	1,279,625,732	1,352,287,296	1,332,241,161	1,320,304,770

National Opioid Shipments by Buyer Business Activity, in MME														
Buyer Business Activity	# of Customers	# of Transactions	Total MME	Annual MME Per Cap	2006	2007	2008	2009	2010	2011	2012	2013	2014	
...	
Grand Total	221,414	271,719,367	1,069,058,007,154	100.0%	384.51	86,383,795,566	97,971,340,469	108,701,088,818	121,194,047,135	134,520,729,017	136,930,437,278	133,599,751,573	126,363,173,394	123,393,643,904

Cabell County and the City of Huntington, WV Opioid Shipments by Buyer Business Activity, in MME														
Buyer Business Activity	# of Customers	# of Transactions	Total MME	Annual MME Per Cap	2006	2007	2008	2009	2010	2011	2012	2013	2014	
...	
Grand Total	144	208,024	1,051,359,367	100.0%	1,168.81	106,434,339	116,321,353	126,820,325	132,338,204	130,764,249	120,583,924	105,648,646	95,208,486	117,239,841

⁶⁴⁴ Report of Craig McCann, Appendix 10 at pp.76, 91, 106.

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2. Between 2006-2014, Defendants AmerisourceBergen, McKesson and Cardinal Health distributed 79,263,830 Total Dosage Units of opioid pain relievers (OPRs) in Cabell County, accounting for 34%, 21% and 17% of the market for OPRs respectively (combined total 72% of the Cabell County market).⁶⁴⁵

Oxycodone and Hydrocodone Total Dosage Units from Distributor Defendants to Dispensers in Cabell County and Huntington City, WV												
Reporter Name	DEA Number	Market Share	Total Dosage Units	2006	2007	2008	2009	2010	2011	2012	2013	2014
AmerisourceBergen Drug Total		34.03%	37,363,600	4,735,720	5,201,780	5,317,210	5,892,900	3,748,660	3,785,260	3,016,080	2,584,790	3,081,200
AmerisourceBergen Drug Corp	RA0314562	33.84%	37,163,540	4,551,360	5,201,780	5,315,110	5,881,300	3,746,660	3,785,260	3,016,080	2,584,790	3,081,200
AmerisourceBergen Drug Corp	RA0289074	0.17%	184,360	184,360	0	0	0	0	0	0	0	0
AmerisourceBergen Drug Corp	RB0363630	0.01%	15,700	0	0	2,100	11,600	2,000	0	0	0	0
McKesson Corporation Total		21.08%	23,153,710	2,625,460	3,056,120	3,650,050	2,404,160	2,104,500	2,277,220	2,206,290	2,036,800	2,793,110
McKesson Corporation	RM0220688	21.08%	23,153,110	2,625,460	3,056,120	3,650,050	2,404,160	2,104,300	2,276,920	2,206,190	2,036,800	2,793,110
McKesson Corporation	PM0001951	0.00%	600	0	0	0	0	200	300	100	0	0
Cardinal Health Total		17.07%	18,746,520	1,119,900	1,058,640	1,159,020	1,283,680	3,202,130	2,800,840	2,821,370	2,636,450	2,664,490
Cardinal Health	RO0153609	17.07%	18,745,920	1,119,900	1,057,140	1,159,020	1,283,680	3,202,130	2,800,840	2,821,370	2,636,450	2,664,490
Cardinal Health 110, LLC	RP0337370	0.00%	1,500	0	1,500	0	0	0	0	0	0	0
Distributor Defendants Total		72.48%	79,263,830	8,481,080	9,316,540	10,126,280	9,580,740	9,055,290	8,863,320	8,043,740	7,258,040	8,538,800

3. As shown below, opioid prescribing in Cabell County and West Virginia significantly exceeded the rate for the United States generally. These rates bore little or no relation to the legitimate needs of the population for pain relief, but instead represent an unnecessary oversupply of addictive drugs.

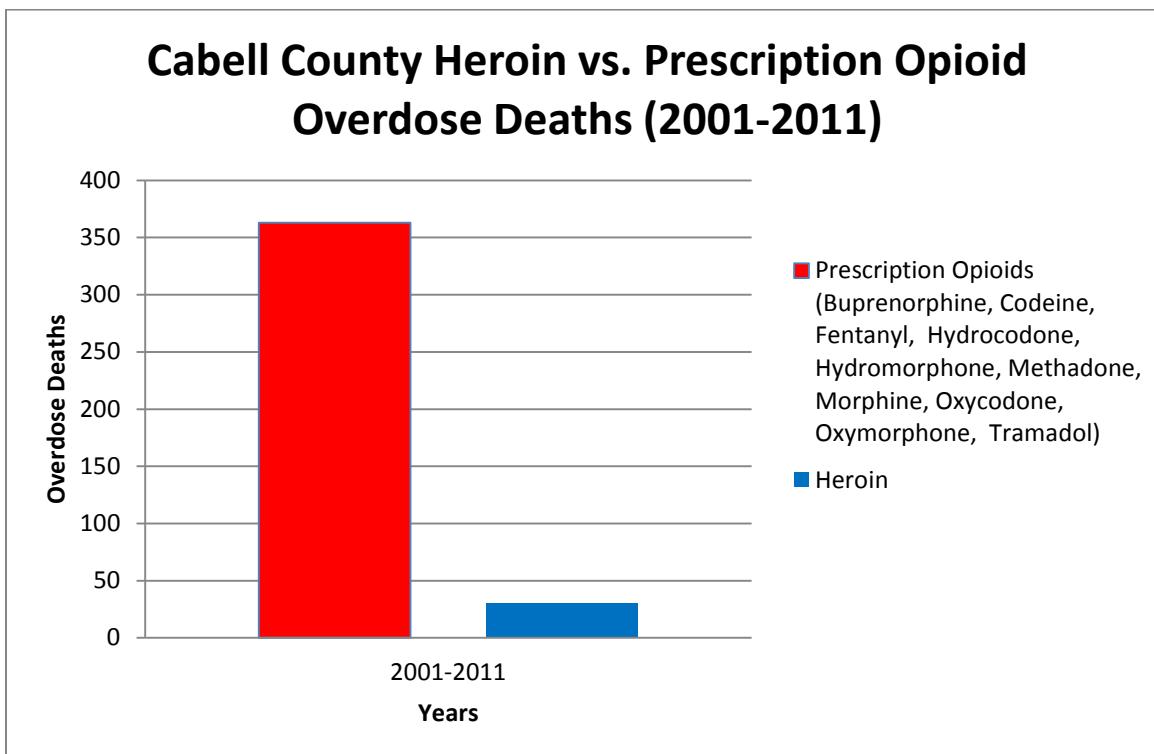
Year	Retail opioid prescriptions dispensed per 100 persons (United States)	Retail opioid prescriptions dispensed per 100 persons (West Virginia)	Retail opioid prescriptions dispensed per 100 persons (Cabell County)
2006	72.4	129.9	175.3
2007	75.9	135.1	194.7
2008	78.2	145.5	209.5
2009	79.5	146.9	205.3
2010	81.2	143.1	194.3
2011	80.9	139.6	186.6
2012	81.3	136.9	167.5
2013	78.1	129.0	149.7
2014	75.6	126.4	148.8
2015	70.6	111.3	135.7
2016	66.5	96.0	122.3
2017	59.0	81.3	106.8
2018	51.4	69.3	92.1

⁶⁴⁵ Report of Craig McCann, Appendix 10 at p. 2436.

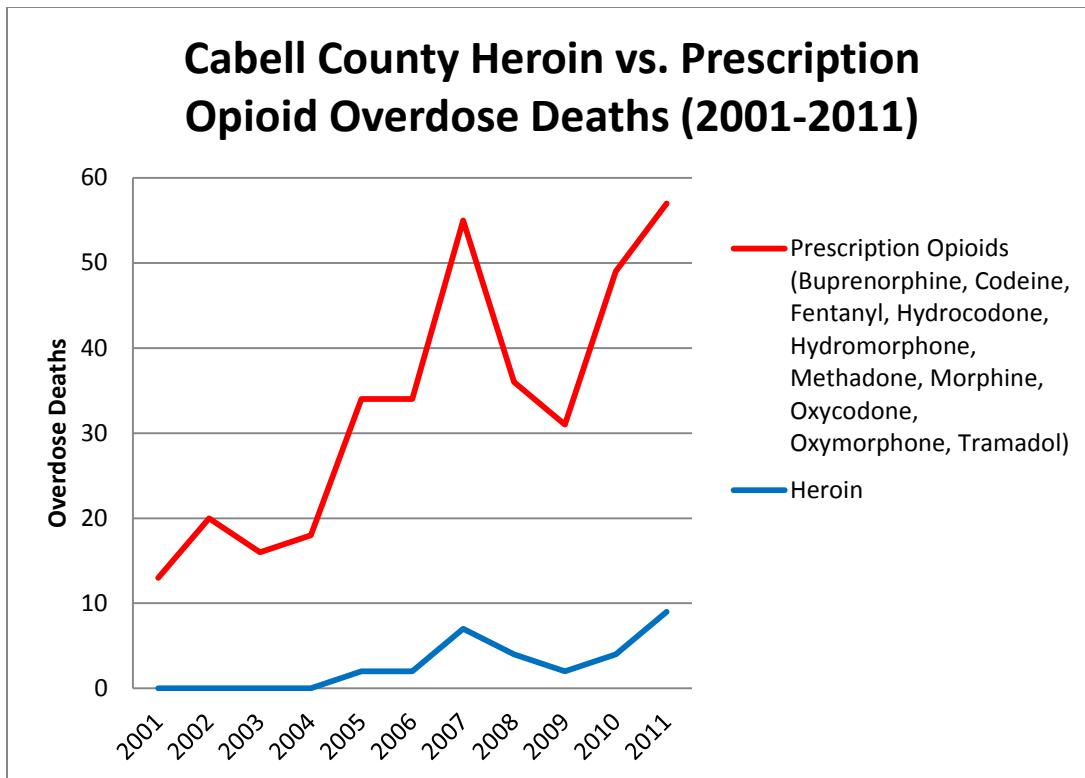
Source: Ctrs. for Disease Control and Prevention. U.S. State and County Opioid Prescribing Rates. Maps, 2006-2018; <https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html>.

C. Opioid Overdose Deaths:

- As shown in the graphs⁶⁴⁶ below, mortality in Cabell County due to prescription opioids greatly exceeded mortality due to heroin during the onset of the opioid epidemic and for many years thereafter, resulting in a population of opioid addicted individuals who transitioned to heroin and later to illicit fentanyl, when those drugs became less expensive or prescription opioids became more difficult to obtain:

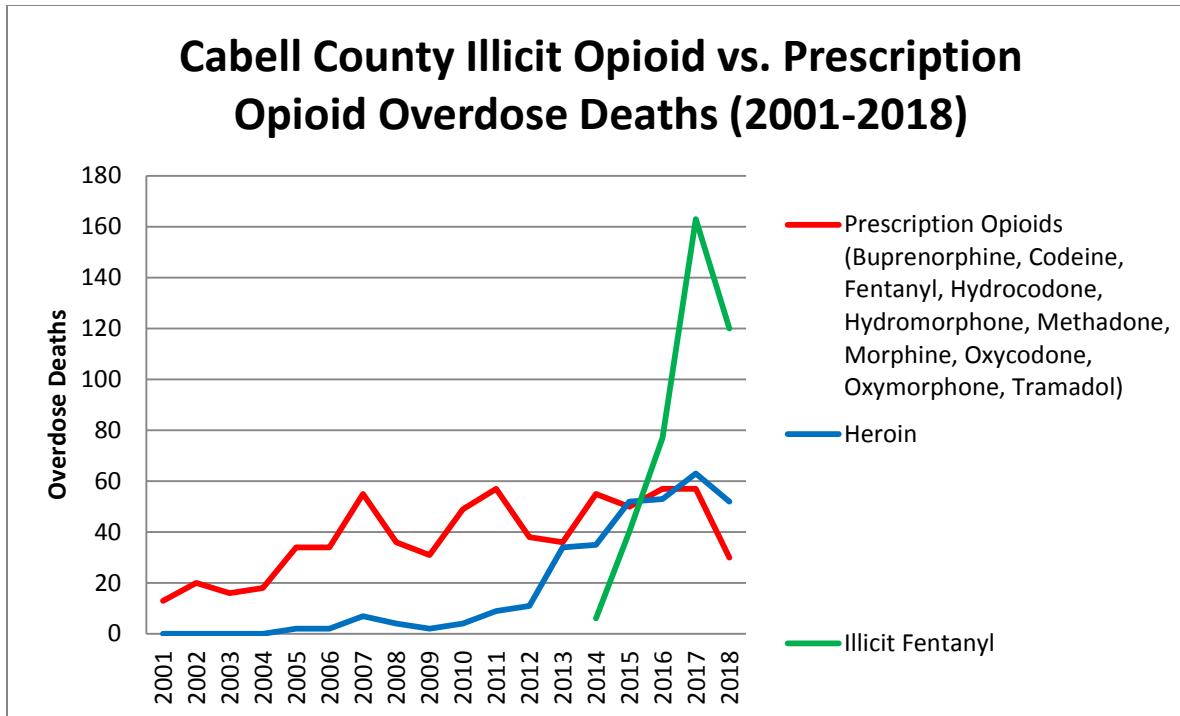


⁶⁴⁶ Based on data in the Report of Gordon Smith.



2. As described in my Report, the second and third waves of the epidemic (heroin and illicit fentanyl) began in more recent years in the US generally, and the graph⁶⁴⁷ below shows that this was also the pattern in Cabell County:

⁶⁴⁷ Based on data in the Report of Gordon Smith.



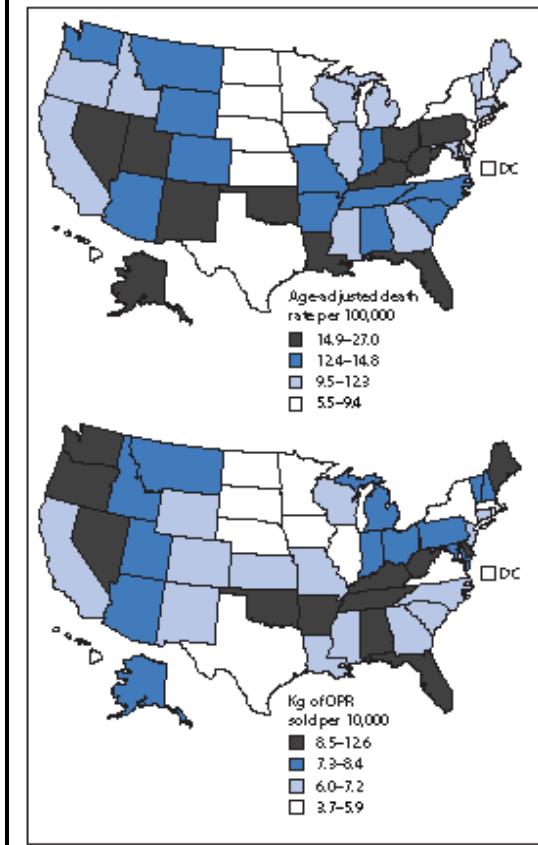
3. A 2011 CDC publication shows that, as of 2008, West Virginia had the second highest opioid pain reliever (OPR) death rate of any state in the United States (25.8 per 100,000 population), which was more than double the national average (11.9 per 100,000 population). (Table 2, below). The same article shows that West Virginia was among the top category for both OPR mortality and OPR sales (Figure 1, below), and that OPR deaths, hospital admissions, and sales increased in parallel between 1999-2010 (Figure 2, below). The CDC article cited as a “Key Point,” that “[d]eath from opioid pain relievers (OPR) is an epidemic in the United States,” and West Virginia was among the most afflicted by that epidemic.⁶⁴⁸

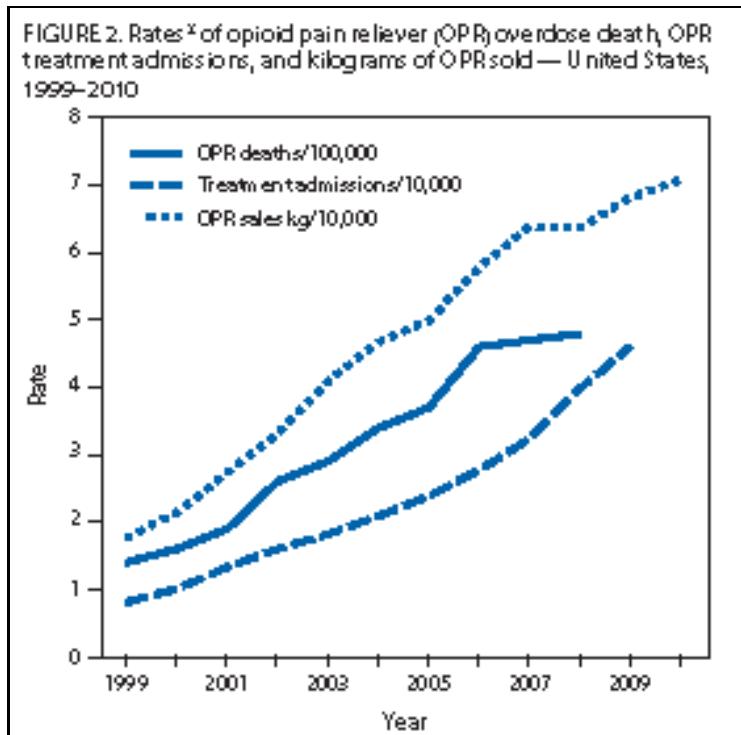
⁶⁴⁸ Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999—2008; MMWR, November 4, 2011 / 60(43);1487-1492.

TABLE 2. Rates of drug overdose death, nonmedical use of opioid pain relievers (OPR), and OPR sales, by state — United States

State	Drug overdose deaths*				OPR			
	Overall	Non-Hispanic whites	Nonmedical use [†]	Sales [§]				
Rate	(SE)	Rate	(SE)	%	(SE)	Rate	(SE)	
National	11.9	(0.1)	14.7	(0.1)	4.8	(0.1)	7.1	(0.0)
New Mexico	27.0	(1.2)	25.1	(1.7)	5.7 [¶]	(0.6)	6.7	(0.2)
West Virginia	25.8	(1.2)	26.6	(1.3)	5.9 [¶]	(0.6)	9.4	(0.2)
Nevada	19.6	(0.9)	27.5	(1.3)	5.9 [¶]	(0.4)	11.8	(0.2)
Utah	18.4	(0.9)	20.4	(1.0)	5.3 [¶]	(0.4)	7.4 [¶]	(0.2)
Alaska	18.1	(1.6)	18.1 [¶]	(2.1)	5.2 [¶]	(0.8)	8.2	(0.3)
Kentucky	17.9	(0.7)	19.6	(0.7)	6.0	(0.3)	9.0	(0.1)
Rhode Island	17.2	(1.3)	19.5	(1.5)	6.1	(0.6)	5.9	(0.2)
Florida	16.5	(0.3)	23.9	(0.5)	4.1	(0.2)	12.6	(0.1)
Oklahoma	15.8	(0.7)	17.5	(0.8)	8.1	(0.3)	9.2	(0.2)
Ohio	15.1	(0.4)	16.0	(0.4)	5.5	(0.2)	7.9	(0.1)
Louisiana	15.0	(0.6)	19.2	(0.8)	5.3 [¶]	(0.3)	6.8	(0.1)
Pennsylvania	15.1	(0.4)	15.6	(0.4)	4.1	(0.2)	8.0	(0.1)
...	
Minnesota	7.2	(0.4)	7.2	(0.4)	4.4 [¶]	(0.2)	4.2	(0.1)
Iowa	7.1	(0.5)	7.5	(0.5)	3.6	(0.3)	4.6	(0.1)
Nebraska	5.5	(0.6)	5.8	(0.7)	3.6	(0.3)	4.2	(0.2)

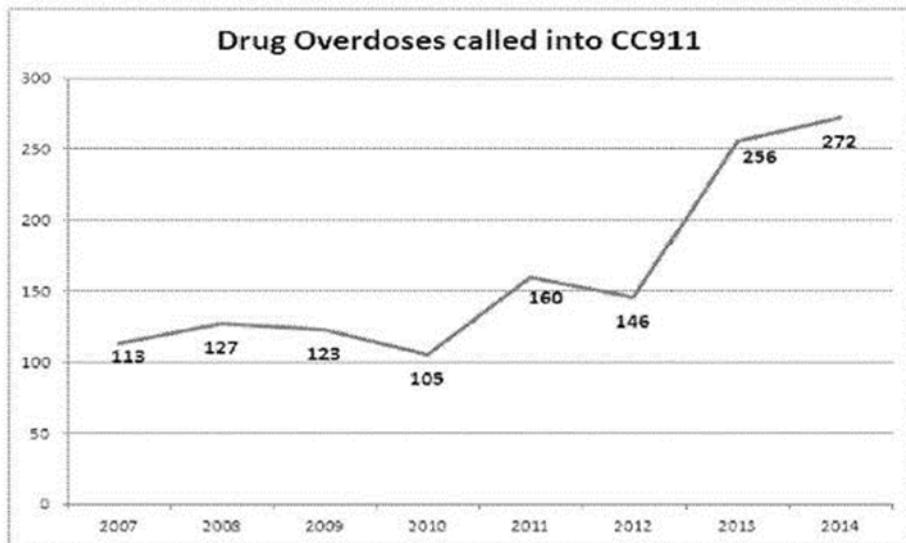
FIGURE 1. Drug overdose death rate in 2008 and rate of kilograms (kg) of opioid pain relievers (OPR) sold in 2010 — United States





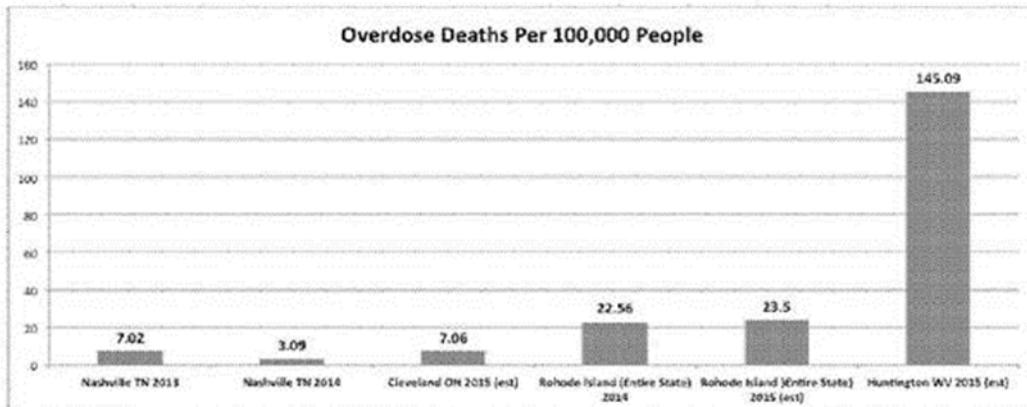
4. Cabell County Community Health Assessment Updates reported on overdose calls and deaths.
 - a. As shown in a graph included in the September 2015 Cabell County Community Health Assessment Update, drug overdoses called in to Cabell County 911 increased from 113 in 2007 to 272 in 2014.⁶⁴⁹

⁶⁴⁹ CHHD_0005048 at 5102.

Figure 84. Drug overdose 911 calls, Cabell County, 2007-2014.

Source: Huntington Mayor's Office on Drug Control Policy, 2015

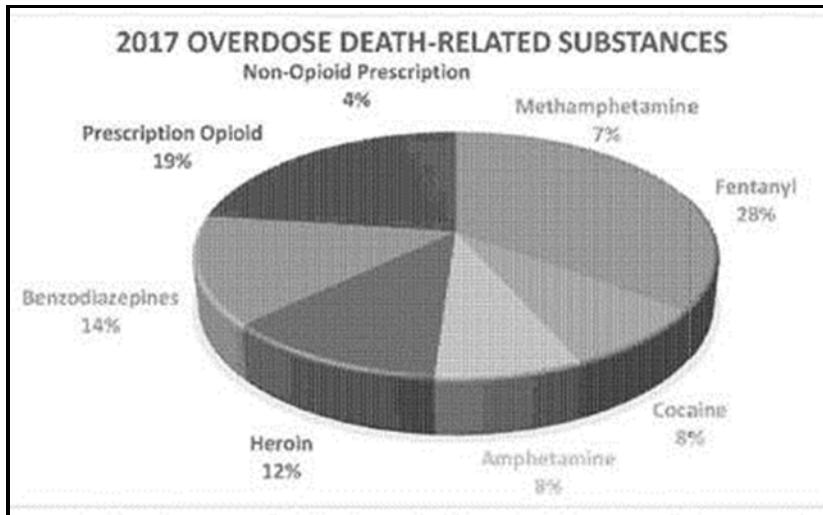
- b. The same health assessment also showed that overdose deaths per 100,000 in Huntington, WV in 2015 were 145.09 compared to 23.5 for the entire state of Rhode Island.⁶⁵⁰

Figure 85. Drug overdose death rates, Huntington compared to other cities, 2014-2015.

Source: Huntington Mayor's Office on Drug Control Policy, 2015

⁶⁵⁰ CHHD_0005048 at 5103.

- c. Charts from the September 2017 Cabell County Community Health Assessment Update showed prescription opioids accounted for 19% of all overdose deaths in West Virginia.⁶⁵¹ An additional 40% were related to heroin and fentanyl, often described as “intertwined with,” or “interrelated to” the OPR epidemic wave that preceded the heroin/fentanyl waves.⁶⁵²

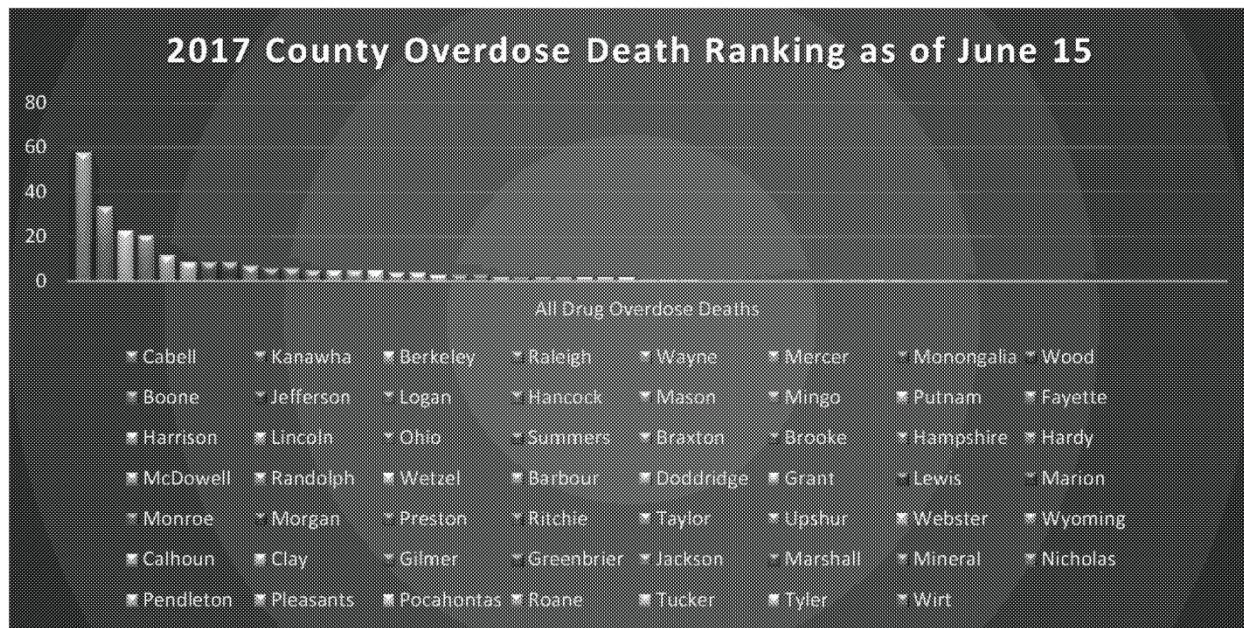


- d. The same Health Assessment also reported Cabell was the #1 ranked county in West Virginia for opioid deaths in 2017 through June 15.⁶⁵³

⁶⁵¹ CHHD_0000871 at 0999.

⁶⁵² See Report at Paragraph C.8, re the Gateway Effect.

⁶⁵³ CHHD_0000871 at 1000.

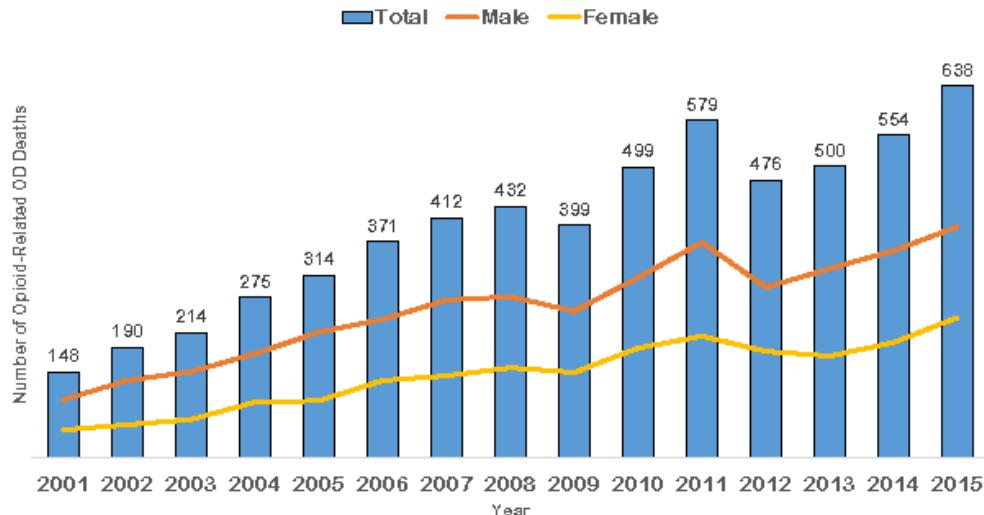


5. In a historical overview the West Virginia Department of Health and Human Resources reported:

- a. Opioid were detected in 6,001 drug deaths in West Virginia form 2001 through 2015, increasing from 148 in 2001 to 638 in 2015.⁶⁵⁴

⁶⁵⁴ West Virginia Drug Overdose Deaths Historical Overview 2001-2015, West Virginia Department of Health and Human Resources, August 17, 2017, at p.7, https://dhhr.wv.gov/oeps/disease/ob/documents/opioid/wv-drug-overdoses-2001_2015.pdf.

Figure 6: Opioid-Related Overdose Deaths, West Virginia Occurrences, 2001-2015 (N=6,001)

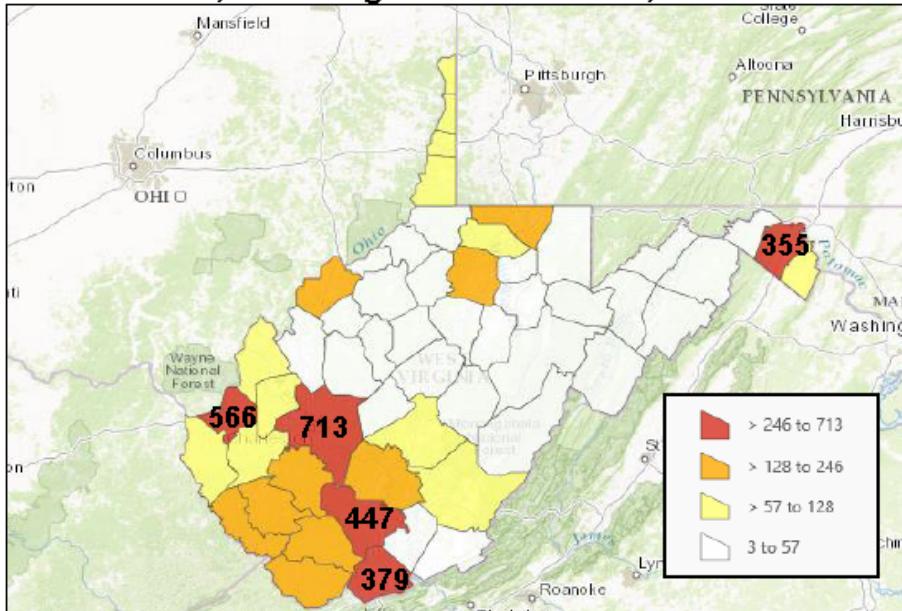


Data Source: WV Health Statistics Center, Vital Statistics System 2015 Preliminary Data

- b. Cabell County accounted for 566 of the opioid-related overdose deaths that occurred in West Virginia from 2001-2015.⁶⁵⁵

⁶⁵⁵ *Id.*

Figure 7: County-Level Distribution of Opioid-Related Overdose Deaths, West Virginia Occurrences, 2001-2015



Data Source: WV Health Statistics Center, Vital Statistics System 2015 Preliminary Data

D. Conclusion:

The data shown above support my opinion that West Virginia, and Cabell County/City of Huntington in particular, were among the hardest hit by the oversupply of opioid pain relievers, igniting the opioid wildfire that continues to the present. It must be noted that data tables of opioid sales beginning in 2006, while important, do not show the full extent of the increased sales that fueled the epidemic, which had begun years earlier. For example, CDC data, reported in the MMWR article cited above, showed a four-fold increase in opioid sales between 1999-2010, and the graph above (Figure 2, Paragraph C.1) appears to show that sales had tripled between 1999-2006, from under 2 kg per 10,000 population to approximately 6 kg per 10,000 population, before reaching approximately 7 kg per 10,000 by 2010. Accordingly, a comparison of OPR sales data from 1999 through 2014 would show an even greater oversupply to West Virginia generally, and Cabell County/Huntington in particular. There is no basis to believe that this oversupply was linked to either increased population or increased experience of pain during the relevant period of time. Instead, these alarming figures indicate the combined effect of misrepresented risks and benefits, failure to monitor the vastly increased supply and exposure, and the highly addictive nature of OPRs.

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Anna Lembke, M.D. Report

APPENDIX IV

Statement of Anna Lembke, MD on the Proper Indication for Opioids

Appendix IV: Statement of Anna Lembke, MD on the Proper Indication for Opioids

A. Chronic Noncancer Pain (CNCP).

The recent, authoritative report of the National Academy of Science, Engineering and Mathematics (NASEM) concluded that “*available evidence does not support the long-term use of opioids for management of chronic noncancer pain.* On the other hand, evidence indicates that patients taking opioids long-term are at increased risk of OUD and opioid overdose, as well as a number of other adverse outcomes.”⁶⁵⁶ I concur. Prescription opioids are not recommended in the treatment of chronic pain. A growing body of evidence demonstrates serious risks of harm with long-term opioid use, made worse with increasing dose and duration. Further, there is no robust evidence for efficacy of opioids in the treatment of pain beyond 12 weeks.⁶⁵⁷ In short, long-term opioid therapy for chronic pain is contrary to the evidence and not good medical practice.

A large and growing body of evidence shows dose and duration-dependent harms caused by chronic opioid therapy, including but not limited to addiction and death.⁶⁵⁸

⁶⁵⁶ National Academies of Science Engineering and Medicine (NASEM). Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use; 2017. doi:10.17226/24781, at p.51 (emphasis added).

⁶⁵⁷ A single RCT of oxycodone and morphine versus placebo was carried out for 16 weeks. Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. Spine (Phila Pa 1976). 1998;23(23):2591-2600. doi:10.1097/00007632-199812010-00014.

⁶⁵⁸ See, e.g., Bohnert, fn. 1, above; Dunn KM, Saunders KW, Rutter CM, *et al.* Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann Intern Med.* 2010;152(2):85-92

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Further, opioids can make pain worse over time through a process called opioid induced hyperalgesia, which is closely linked to neuroadaptation and tolerance.

The claims of benefits of long-term opioids for chronic pain are based on low quality, anecdotal evidence, and contrary to the randomized controlled trial (RCT) evidence and consensus views. A recent meta-analysis by Busse, et al., assessed available RCTs of opioids, finding that compared to placebo, the difference in pain relief did not meet a pre-specified “Minimally Important Difference” (MID), defined as “the smallest amount of improvement in a treatment outcome that patients would recognize as important.”⁶⁵⁹ Nevertheless, the authors stated that approximately 12% percent of chronic pain patients might choose to evaluate whether, in their individual experience, opioids might provide improved pain relief compared to other medications, despite the known, increased risk of opioids, an assertion that is not supported by their data.⁶⁶⁰

The NASEM Report’s conclusion was subsequently reinforced by the 2018 publication of the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) study in the *Journal of the American Medical Association*, by Krebs, et al. As the only long-term, RCT of chronic opioid therapy compared to non-opioid pain

⁶⁵⁹ Busse JW, Wang L, Kamaleldin M. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. *JAMA*. 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472.

⁶⁶⁰ According to the CDC, approximately 3-4% of prescription opioid users take these drugs for long-term treatment of pain. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 2016;15(15):1624–1645. Therefore, the number of opioid users who might choose to evaluate whether opioids provide greater pain relief would be 12% x of the approximately 3.5% who use opioids for chronic pain, or 0.4% of all opioid users.

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medications, it provides the best available evidence on the subject. The SPACE trial found that non-opioid medications (for example nonsteroidal anti-inflammatory drugs such as naproxen or acetaminophen) provide equivalent or greater pain relief compared to opioids, while opioids confer significantly greater risks, leading Krebs et al. to conclude that chronic opioid therapy is not advisable.⁶⁶¹

As a clinician, I have treated hundreds of patients with chronic pain for associated conditions of opioid misuse, dependence, and OUD. My experience is consistent with the authorities referenced above, in that the claimed benefits of long-term opioid therapy for chronic pain do not outweigh the risks; to the contrary, when patients successfully followed a compassionate, patient-centered tapering program to reduce or cease opioid therapy, they reported improvement in their overall well-being and level of pain, and none reported worsening of pain except for the pain of withdrawal from the opioids themselves, which was time-limited.

Based on the consensus view stated in the NASEM Report, research findings, and my own clinical experience, it is my view that at a population level, the risks of long-term opioids for chronic pain far outweigh the benefits. For very few patients, benefits might outweigh the risks; but even then risks increase with higher dose and longer duration of

⁶⁶¹ Krebs et al., “Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients with Chronic Back Pain or Hip or Knee Osteoarthritis Pain the SPACE Randomized Clinical Trial,” *JAMA - J Am Med Assoc.* 2018. doi:10.1001/jama.2018.0899, at p.872.

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opioid treatment, such that risks may eventually exceed any small possible benefit over other less dangerous pain reduction strategies.

B. Whether or Not Pain is “Undertreated,” Opioids Are Not the Solution

The epidemic of opioid over-prescribing in the past 25 years was fueled, in part, by industry assertions that chronic pain was “undertreated” in the United States. On this subject, I agree with the conclusion in the NASEM Report: “The very real problems of underdiagnosis and undertreatment of pain are valid concerns, but *it would be a mistake to infer that greater utilization of opioids would ameliorate these problems.*”⁶⁶² This conclusion follows directly from NASEM’s conclusion that evidence does not support efficacy of long-term opioids for chronic pain, while the risks of such therapy are significant and well-established.

There are many estimates of the prevalence of chronic pain in the United States, which vary depending on the definitions of the investigators. A reasonable, recent estimate is found in an article by Pitcher, et al., sponsored by the National Institutes of Health as a part of the “National Pain Strategy” (NPS), which reported overall Chronic Pain at 18.4%, and High Impact Chronic Pain (HICP) at 4.8%.⁶⁶³ The NPS defines HICP as the experience of pain on most days over the past 3 months, with concomitant limitations on activities due to pain. To the extent that long-term opioid therapy would

⁶⁶² NASEM Report (2017) at p. 51. (emphasis added).

⁶⁶³ Pitcher MH, Von Korff M, Bushnell MC, Porter L. Prevalence and Profile of High-Impact Chronic Pain in the United States. J Pain. 2019;20(2):146-160. doi:10.1016/j.jpain.2018.07.006.

ever be warranted, it is my opinion that only the severity of HICP might justify imposing the known risks of long-term opioid treatment.

C. Tapering Is Appropriate for Opioid Dependence and OUD

After nearly three decades of opioid overprescribing, we now find ourselves in the lamentable situation wherein millions of Americans are physiologically dependent on opioids, some of whom may never be able to taper down and/or off of opioids, due to irreversible neuroadaptation. The most compassionate approach to these patients is a slow, patient-centered opioid taper.⁶⁶⁴ In cases of severe prescription opioid dependence where opioid tapering fails, continuing opioids at low and closely monitored doses may be the most compassionate harm-reduction approach.⁶⁶⁵

D. Non-opioids Have Been Found to Be Equivalent or Superior to Opioids in Many Acute Pain Settings.

Opioids are indicated for short-term use (days to weeks, up to 90 days) in the management of acute pain (e.g., trauma, dental procedures, and post-surgery). However, there are numerous studies finding that non-opioids provide equivalent pain relief with lower risk. For example, a 2018 study of dental pain by Moore, et al., found non-opioids superior to opioids: “The best available data suggested that the use of nonsteroidal medications, with or without acetaminophen, offered the most favorable balance between

⁶⁶⁴ Lembke, “BRAVO! A Collaborative Approach to Opioid Tapering.”, Oregon Pain Guidance, March 2020, <https://www.oregonpainguidance.org/wp-content/uploads/2020/03/BRAVO-FINAL-3.13.20-1.pdf>

⁶⁶⁵ Chou, R., Ballantyne, J., Lembke, A., Rethinking Opioid Dose Tapering, Prescription Opioid Dependence, and Indications for Buprenorphine, Annals of Internal Medicine, 2019; doi:10.7326/M19-1488

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benefits and harms, optimizing efficacy while minimizing acute adverse events.”⁶⁶⁶ The Moore study supports that opioids are not an appropriate choice for dental pain, according to evidence-based principles comparing risks and benefits. Nonetheless, a recent survey found that 23% of patients who received an opioid prescription in a one-year period were prescribed opioids by a dentist or oral surgeon.⁶⁶⁷

Opioids are also commonly prescribed for the pain of acute trauma in emergency medicine. However, the results of a recent study of opioids and non-opioid pain relievers in emergency care concluded that “there are no clinically meaningful differences between the analgesic effects of these 4 analgesics and suggest that a combination of ibuprofen and acetaminophen represents an alternative to oral opioid analgesics for the treatment of acute extremity pain in the ED,” and that nonopioid patients experienced greater pain relief with fewer adverse events.⁶⁶⁸

In the context of post-surgery treatment, numerous studies have found that non-opioids can be substituted for opioids, or that the number of opioids prescribed post-surgery can be substantially reduced, with equivalent pain relief. For example, in a study in which patients were treated with Tylenol/ibuprofen after parathyroid and thyroid surgery, the authors

⁶⁶⁶ Moore, et al., Benefits and harms associated with analgesic medications used in the management of acute dental pain. 2018; 149: 256-263, *J Am Dental Assoc.* 2018; 149: 256-265.

⁶⁶⁷ Press Release: One-Third of Americans Have Received an Opioid Prescription in the Past Two Years, NORC at the University of Chicago, September 27, 2018.

<https://www.norc.org/NewsEventsPublications/PressReleases/Pages/one-third-of-americans-have-received-an-opioid-prescription-in-the-past-two-years.aspx>

⁶⁶⁸ Chang, Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. *JAMA* 2017; 318:1661-1667.

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concluded that such patients “need very little, if any, post-operative opioids.... Decreasing the volume of opioid medications prescribed at discharge will decrease waste and reduce potential for addiction.”⁶⁶⁹ Other authors stated, “ we have completely stopped prescribing opioids” for cervical neck operations, and reduced Norco (acetaminophen + 5mg hydrocodone) prescribing from 40 pills down to 5 pills for adrenalectomy, finding that non-opioid medications provided comparable pain relief; they concluded that perioperative and post-surgery opioid use is “less about inherent pain associated with operations, but more about misperceptions and biases that both physicians and patients have about post-operative pain and required management.”⁶⁷⁰

Based on the state of scientific inquiry, the CDC has found the evidence sufficient to support the conclusion that naproxen, an NSAID, is as effective as opioids for acute pain, and with lower risk of adverse effects.⁶⁷¹

E. Risk of Persistent Use following Opioids for Acute Pain

There is a consensus that opioids for acute pain lead to persistent use among 5 to 13% of short-term users, with most studies reporting toward the higher figure, and there is significant concern over such persistent use after initiating conditions have abated.⁶⁷² This

⁶⁶⁹ Shindo M, Lim J, Leon E, Moneta L, Li R, Quintinalla-Diek L. Opioid Prescribing Practice and Needs in Thyroid and Parathyroid Surgery. *JAMA Otolaryngology - Head and Neck Surgery*. 2018; at p. 1102.

⁶⁷⁰ Kuo JH, et al. Use and Misuse of Opioids after Endocrine Surgery Operations. *Annals of Surgery*. 2020;1-6.

⁶⁷¹ Opioids for Acute Pain: Get the Facts, Ctrs. for Disease Control and Prevention.
<https://www.cdc.gov/drugoverdose/pdf/patients/Get-the-Facts-a.pdf>

⁶⁷² See, e.g., Deyo RA et al. Use of Prescription Opioids Before and After an Operation for Chronic Pain (lumber fusion surgery). *Pain*. 2018 Jun;159(6):1147-1154. doi: 10.1097/j.pain.0000000000001202, at p. 5 (13% persistent users); Cook DJ et al. Benchmarks of Duration and Magnitude of Opioid Consumption After Total Hip and Knee Arthroplasty: a database analysis of 69,368 patients. *J. Arthroplasty*. 2019; 34: 638-644, at p. 638 (10-13%).

subset of patients receives no benefit from continued opioid use, since the initiating painful condition is no longer in need of treatment; instead, such patients have become dependent and are at increased risk of OUD and mortality due to the known exacerbation of risk with longer duration of exposure.

F. Over-prescribing for Acute Pain Is a Source of Diversion

Additional harms of overprescribing for acute pain arise from the fact that patients commonly do not use all of the pills prescribed for their condition, since they are not needed for pain relief, or because of adverse side effects. The unused pills become a source of sale, gift, theft, or barter, to individuals for whom the drugs were not prescribed, and who are by definition misusing the opioids to maintain a habit, or to get high.⁶⁷³

G. Opioid Use for Specific Painful Disease States

Opioids are indicated for treatment of certain painful diseases (e.g., sickle cell crisis, post-herpetic neuralgia (PHN)),⁶⁷⁴ end-of-life suffering (hospice care). Opioids are also indicated for cancer pain, based in significant part on the expectation that cancer

⁶⁷³ National Academies of Sciences, Engineering, and Medicine (NASEM 2020). 2020. *Framing Opioid Prescribing Guidelines for Acute Pain: Developing the Evidence*. Washington, DC: The National Academies Press..<https://www.nap.edu/catalog/25555/framing-opioid-prescribing-guidelines-for-acute-pain-developing-the-evidence>, at p.26.

⁶⁷⁴ Sickle cell disease affects 100,000 Americans, and 1 of every 365 Americans of African descent. Data & Statistics on Sickle Cell Disease, Ctrs. For Disease Control and Prevention, <https://www.cdc.gov/ncbddd/sicklecell/data.html> (last reviewed October 21, 2019) . Approximately 1 million cases of herpes zoster (HZ, or “shingles”) occur annually in the US; it is estimated that 5%–20% of those with HZ go on to develop PHN. Malick-Searle, Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. *Journal of Multidisciplinary Healthcare* 2016;9 :447–454.

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patients have a limited life expectancy, and that the risks of Opioid Use Disorder (OUD) and mortality are outweighed by the benefits of pain relief. However, with advanced treatment methods, more cancer patients are surviving for longer periods of time, and the risks of addiction and overdose mortality among cancer patients have been identified in the peer-reviewed medical literature⁶⁷⁵ Thus, even in the setting of cancer pain, caution should be exercised to treat with the lowest dose for the shortest time, and to treat with low dose opioids intermittently rather than continuously, to reduce the risks of OUD and mortality.

H. Conclusion

The adverse effects of opioids are well-known and devastating. These include dependence, opioid use disorder (OUD)/addiction, overdose mortality, primarily due to respiratory suppression, non-fatal overdose, and neonatal abstinence syndrome (NAS), which afflicts newborns well into childhood. These conditions are severe, fatal or life-threatening, permanent or of long duration. The Cabell Huntington Community has been even more severely impacted than the US as a whole.

In contrast, the benefits of prescription opioids are limited or ephemeral. I agree with the consensus of leading authorities that there is no reliable evidence that long-term

⁶⁷⁵ For example, the Bohnert study found a hazard ratio (HR) of 11.99 for opioid-associated mortality among cancer patients exposed to 100 mg MME opioids, compared to those exposed to 1-20 mg, and this HR exceeded even the significantly elevated HR for patients with acute and chronic pain conditions. Bohnert ASB, Valenstein M, Bair MJ, *et al.* Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA - J Am Med Assoc.* 2011;305(13):1315-1321, at p. 1315

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opioids provide clinically significant relief of CNCP, and the best evidence supports equivalent pain relief and fewer risks with non-opioids such as NSAIDs. Although opioids are indicated for acute pain, numerous studies show equivalent relief and lower risk with non-opioids; a significant minority of acute-pain opioid patients go on to become persistent users who suffer dependency but do not benefit from opioid use; over-prescribing for acute conditions results in diversion to inappropriate users, a source of community harm that further offsets any pain relief benefits to appropriate users; and the pain relief in acute conditions is inherently brief, compared to the long-term or permanent harms of fatal and non-fatal overdose, OUD and NAS.

In summary, it is my clinical opinion that the harms of prescription opioids to the Cabell Huntington Community far outweigh any benefits that may be conferred.

Anna Lembke, M.D. Report

APPENDIX V

Summary of BRAVO Protocol

Appendix V: Summary of BRAVO Protocol

Broaching the Subject

- Involve the patient
- Take more time
- Get the support of your team
- Use motivational interviewing (reflection, validation, support)
- For inherited patients, maintain the current dose and document if considering a taper

Risk Benefit Assessment

- Consider tapering for the following reasons:
- Patient request
- Pain and function not improved
- Adverse opioid effects
- Co-occurring conditions (including mental health)
- Dose over 90 MED
- Concurrent sedatives
- Opioid use disorder
- Opioid overdose

Addiction and Dependence Happen

- Addiction = The 3 C's: *Control, Craving*, continued use despite *Consequences*
- Dependence = Tolerance, withdrawal, without the 3 C's
- Anyone can become addicted or dependent
- Reassure patients there is effective treatment for both
- Consider buprenorphine

Velocity and Validation

- Go slowly (*Tapering Examples*)
- Maintain the same schedule (BID, TID)
- Let the patient drive “*Which opioid would you like to taper first?*”
- Take breaks, but never go backwards
- Warn patients that pain gets worse before it gets better
- Validate that opioid tapering is hard

Other Strategies for Coping with Pain

- Help patients understand how pain works
- Encourage regular, restful sleep
- Promote healthy activities
- Maintain a positive mood
- Foster social connections

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- Make good nutritional choices
- Consider non-opioid pain medications

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EXHIBIT A

Curriculum Vitae and List of Publications

*Lembke Report**Confidential — Subject to Protective Order***Anna Lembke, M.D.**

Associate Professor of Psychiatry and Behavioral Sciences (Primary Appointment)

Anesthesiology and Pain Medicine (Courtesy Appointment)

Stanford University School of Medicine

Department of Psychiatry and Behavioral Sciences

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alembke@stanford.edu

*Last updated (July 23, 2020)***Education and Training**1985-1989 Yale University (BA, Humanities; *summa cum laude*)
New Haven, CT1989-1990 University of Beijing (Mandarin Chinese)
Beijing, China1992-1995 Stanford University School of Medicine (MD)
Stanford, CAA.
1995-1997 Residency, Pathology
Stanford University School of Medicine, Stanford, CA1997-1998 Internship, Internal Medicine
Highland Hospital, Alameda, CA1998-2000 Residency, Psychiatry
Stanford University School of Medicine, Stanford, CA2000-2002 Fellowship in Mood Disorders, Psychiatry and Behavioral Sciences
Stanford University School of Medicine, Stanford, CA**Honors and Awards**1989 *Summa cum laude* in Humanities
Yale University1989 Outstanding Contributor to Community Life
Yale University

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1989	Yale-China Fellowship Yale University
1995	Outstanding Teacher in Structural Biology Stanford University School of Medicine
1999	Outstanding Research in Severe Mental Illness Janssen Scholar
2000	Travel Scholarship Medical Education and Research Foundation (MERF)
2000	Outstanding Research in Severe Mental Illness American Psychiatric Association
2002	Laughlin Fellowship American College of Psychiatrists
2009	Travel Scholarship Alcohol Medical Scholars Program
2011	Travel Scholarship Association of Medical Education, Research, Substance Abuse
2013	Faculty Fellowship Stanford University School of Medicine
2014	Excellence in Academic Teaching Stanford University School of Medicine
2015	Chairman's Clinical Innovation Award Stanford University School of Medicine
2017	Distinguished Visiting Professorship Johns Hopkins Bayview, Department of Internal Medicine
2018	Distinguished Flexner's Dean Lecturer Vanderbilt University School of Medicine
2018	Distinguished Marcel Malden Lecturer Tacoma, Washington
2018	Distinguished Alpha Omega Alpha Visiting Professorship University of Kansas School of Medicine

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- 2018 Distinguished Alumni Award
Evanston Township High School, Evanston, IL
- 2018 Excellence in Academic Teaching Award
Stanford University School of Medicine
- 2019 Distinguished Baldwin Lecturer
The Accreditation Council for Graduate Medical Education (ACGME)
- 2019 Distinguished Tector Lecturer
69th Annual Course for Family Physicians, Montreal, Canada
- 2019 Distinguished James Platt White Memorial Lecturer
Buffalo, New York OB/GYN Society
- 2019 Distinguished Crowley Lecturer
Lucile Packard Children's Hospital, Stanford University
- 2019 Distinguished University of Tampa Honors Symposium Lecturer
University of Tampa, Florida
- 2019 Distinguished Evelyn G. Keever Bioethics Day Lecturer
Eastern Virginia Medical School, Virginia
- 2020 Fellowship Training Directors Award
American Society of Addiction Medicine
- 2020 Hazelden Betty Ford Foundation Humanitarian Kelly Clark Spirit Award
Hazelden Betty Ford Foundation, Portland, Oregon
- 2020 Irma Bland MD Certificate of Excellence in Teaching Residents
American Psychiatric Association
- 2021 Distinguished Alpha Omega Alpha Visiting Professorship
University of Nevada, Reno School of Medicine

Academic and Clinical Appointments***Stanford University School of Medicine***

- 2012-present Chief, Addiction Medicine Dual Diagnosis Clinic

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	Department of Psychiatry and Behavioral Sciences
2013-present	Program Director, Addiction Medicine Fellowship Department of Psychiatry and Behavioral Sciences
2016-present	Courtesy Appointment Department of Anesthesiology and Pain Medicine
2017-present	Medical Director, Addiction Medicine Stanford Health Care and Stanford University Hospital
7/2017-6/2022	Associate Professor of Psychiatry and Behavioral Sciences
5/2010-4/2017	Assistant Professor of Psychiatry and Behavioral Sciences
9/2003-4/2010	Instructor Department of Psychiatry and Behavioral Sciences

Other Previous Employment

1991-1992	Bilingual Teacher (grades K-8), State Certified in Chinese (Mandarin) Healy Elementary School, Chicago, IL
1989-1990	English Teacher, Yali Middle School Changsha, China

Medical Licensure and Specialty Board Certification

1995	California medical license #A62241
2003	Diplomate, American Board of Psychiatry and Neurology Certificate #51988; recertified 2/18/2013
2012	Diplomate, American Board of Addiction Medicine Certificate #2012288; certified 12/15/2012 (Exp date 12/31/2022)
2013	DEA-X waivered to prescribe buprenorphine products

Educational Leadership

2003-2005	Chair, Curriculum Committee Department of Psychiatry and Behavioral Sciences Stanford University School of Medicine
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- 2009-present Course Director, CME-accredited monthly Stanford seminar series for community physicians - “Closing the Gap: Moving towards Best Practices in Psychiatry”
- 2012-2014 Principal Organizer and Lecturer of the free Buprenorphine Certification Course and CURES registration for Stanford University
- 2013-present Program Director, Addiction Medicine Fellowship
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
- 2014 Expert Consultant, Alcohol and Women Task Force
Office of the Vice Provost for Student Affairs, Stanford University
- 2014-2016 Annual Medical Student Town Hall Meetings on Wellness and Professionalism (Issues of Substance Use and Addiction)
Office of the Dean of the School of Medicine, Stanford University
- 2015-2016 Expert Consultant, Alcohol and Other Drug (AOD) Subcommittee of the Mental Health and Well-Being Advisory Committee
Stanford University
- 2016-present Chair, Addiction Medicine Task Force
Stanford University School of Medicine
(Goal: create a new curriculum for addiction/safe opioid prescribing)
- 2017-present Committee on Professionalism
Stanford University School of Medicine

Teaching and Mentoring

Stanford University School of Medicine Ongoing Lecture Series

- 2002-present Course Director, Addiction Medicine, Stanford University School of Medicine
- 2009-present Course Director, Stanford CME series “Closing the Gap in Psychiatry”
- 2012-present Course Lecturer, Substance Use Disorders, Stanford Child Psychiatry Fellowship
- 2012-present Course Lecturer, Substance Use Disorders, Stanford Palliative Care Fellowship
- 2012/’14/’16 Biennial lecture on addiction medicine to Stanford undergraduates as part of the Hum Bio Molecular and Cellular Physiology 256 seminar

*Lembke Report**Confidential — Subject to Protective Order****Stanford University School of Medicine Clinical Supervision (weekly year round)***

2002-present	Inpatient Psychiatry	Medical Students, Residents/Fellows
2010-present	Addiction Med/Dual Dx Clinic	Medical Students, Residents/Fellows
2013-present	Pain and Addiction Clinic	Addiction Medicine/Pain Fellows

Stanford University School of Medicine Addiction Medicine Fellows Advisor

2013-14	Stacie Solt, MD, Emergency Medical and Addiction Medicine, now at San Mateo Medical Center, San Mateo, CA
2014-15	Mitika Kanabar, MD, Family Medicine Physician and Addiction Medicine, now at Southern California Permanente Medical Group, Lancaster, CA
2015-16	Chinyere Ogbonna, MD, Family Medicine, Psychiatry, and Addiction Medicine, now Medical Director of Chemical Dependency Services at Kaiser Permanente, San Jose, CA
2016-17	Rachel Sussman, MD, Family Medicine and Addiction Medicine, now Assistant Professor at Stanford School of Medicine and Indian Health Center/O'Connor, San Jose, CA
2017-18	Amer Raheemullah, MD, Internal Medicine and Addiction Medicine, now Assistant Professor and Director of the Inpatient Addiction Medicine Consult Service at Stanford School of Medicine, Stanford, CA
2017-18	Anusha Chandrakanthan, MD, Family Medicine and Addiction Medicine, now Adjunct Clinical Assistant Professor in Addiction Medicine at Stanford University School of Medicine, Stanford, CA, and Staff Physician at Valley Homeless Health, San Jose, CA
2018-19	Huiqiong Deng, MD, PhD, Psychiatry and Addiction Medicine, now Assistant Professor in Addiction Medicine at Stanford University School of Medicine, Stanford, CA
2018-19	Michael Polignano, MD, Psychiatry and Addiction Medicine, now Assistant Professor in Addiction Medicine at Stanford University School of Medicine, Stanford, CA

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2019-20 Ori Ben-hamou, MD, Psychiatry and Addiction Medicine, Stanford Addiction Medicine Fellowship, Stanford, CA

2019-20 Nathaniel Lepp, MD, Family Medicine and Addiction Medicine, Stanford Addiction Medicine Fellowship, Stanford, CA

Stanford University School of Medicine MedScholars Advisor

2016 MedScholar Advisor for Inbar Raber, *Qualitative Assessment of Clerkship Students' Perspectives of Pain and Addiction Curriculum at Stanford*, Stanford University School of Medicine, Stanford, California

2017 MedScholar Advisor for Alex Ball, *Developing the Addiction Curriculum at Stanford*, Stanford University School of Medicine, Stanford, California

2019 MedScholar Advisor for Emily Keamy-Minor, *Alcohol Screening for Patients Receiving Prescriptions for Benzodiazepines and Opioids*, Stanford University School of Medicine, Stanford, California

Stanford University School of Medicine Junior Faculty Advisor

2016 -2020 Junior Faculty Advisor for Yasmin Owusu, MD in the development of the POM Curriculum for Stanford Medical Students, Stanford University School of Medicine, Stanford, California

Stanford University and Palo Alto University PsyD Consortium Dissertation Review

2016 Dissertation Advisor and Review Committee Member for Jennifer Bielenberg, *Addiction and Stigma*, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

2017 Dissertation Chair and Review Committee Chair for Shelby Schwartz, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

2018 Dissertation Chair and Review Committee Chair for Julia Yasser, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

2020 Dissertation Committee, Sarah Krasner, *Gender Differences in Cannabis Vaporizer Use*, PsyD Consortium, Department of Psychiatry and Behavioral

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Sciences, Stanford University School of Medicine, Stanford, California

- 2020 Dissertation Committee, Rebecca Rothberg, *Harm Reduction and Addiction Treatment*, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California
- 2020 Dissertation Chair and Review Committee Chair for Benjamin Greenberg, *Shared Medical Appointments for Buprenorphine Prescribing for Individuals with Opioid Use Disorder: A Qualitative Study*, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

Professional Associations

- 2011-present Member, American Society of Addiction Medicine (ASAM)
- 2011-present Member, California Society of Addiction Medicine (CSAM)
- 2011-2016 Member, Association of Medical Education and Research in Substance Abuse (AMERSA)
- 2019-present Member, American Psychiatric Association

Regional and National Service

Professional Societies and Advisory Boards and Committees

- 2012-2015 Facilitator, California Society of Addiction Medicine (CSAM) Annual Conference, San Francisco, California
- 2013-2014 Advisor, American Board of Addiction Medicine Practice Improvement and Performance Measures Action Group (PIP MAG)
- 2013-2018 Advisor, American Board of Addiction Medicine Fellowship Development Working Group
- 2013-2019 Board Member, Medical Education and Research Foundation (MERF) for the Treatment of Addiction
- 2013-2020 Member, Public Policy Committee, CSAM
- 2014-2020 Member, California Society of Addiction Medicine Education Committee

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- 2014-2018 Member, California Society of Addiction Medicine Conference Planning
- 2015-2019 Board Member, California Society of Addiction Medicine
- 2015-2016 Representative, American Society of Addiction Medicine PCORI Workshop: *Long-Term Use of Opioids for Chronic Pain*
- 2015-2017 Representative, Appointed by Governor Jerry Brown to the Research Advisory Panel of California, January 2015
- 2015-2019 Member, Public Policy Committee, American Society of Addiction Medicine
- 2015-2016 Chair, Conference Planning Committee, California Society of Addiction Medicine Annual Conference
- 2016-2017 Vice-Chair, Conference Planning Committee, California Society of Addiction Medicine Annual Conference
- 2016-2020 Member, Physicians for Responsible Opioid Prescribing (PROP)
- 2016-2018 President, Addiction Medicine Fellowship Directors Association (AMFDA)
- 2019 Advisor, Task force for The Center on Addiction (a merger between Partnership for Drug Free Kids and CASA Columbia)
- 2019-2023 Board Member, American College of Academic Addiction Medicine

Editorial Work

- 2003-2004 Guest Editor, *Academic Psychiatry*, Issue on Women in Academia
- 2013-2014 Reviewer, *How to Find Quality Addiction Treatment*, CASAColumbia
- 2014-2017 Associate Editor, *Addiction Science and Clinical Practice (ASCP)*

Ad-Hoc Manuscript/Report Review

Academic Psychiatry
Addiction
Addiction Science and Clinical Practice
Agency for Healthcare Research and Quality (AHRQ)
American Journal of Psychiatry
Annals of Internal Medicine

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Archives of General Psychiatry
Asian Journal of Psychiatry
Biological Psychiatry
Bipolar Disorder
British Medical Journal
Culture, Medicine, and Psychiatry
Current Biomarker Findings
Drugs: Education, Prevention & Policy
Expert Opinion on Pharmacotherapy
Expert Review of Neurotherapeutics
General Hospital Psychiatry
Healthcare: The Journal of Delivery Science and Innovation
Journal of Addiction Science and Clinical Practice
Journal of Affective Disorders
Journal of the American Medical Association
Journal of Psychiatric Research
Journal of Studies on Alcohol and Drugs
Medical Journal of Australia
New England Journal of Medicine
New Recovery Community Institutions
Pain Medicine
Psychological Medicine
Rationality and Society
Sociologic Forum
Substance Abuse
Substance Use and Misuse

Current Funding

- 7/20-6/25 Funder: Health Resources and Services Administration (HRSA), \$1,452,178, 0.1
 Calendar
 Title: Addiction Medicine Fellowship
 Purpose: Stanford University Department of Psychiatry proposes to expand its existing Addiction Medicine Fellowship by two fellows in medically underserved communities in Santa Clara County
 Role: Principal Investigator/Project Director (CoPI: Louie)
- 7/20-6/24 Funder: NIDA, \$1,050,000, 0.1 Calendar
 Title: Western Node of NIDA Clinical Trials Network
 Purpose: Oregon Health Sciences University, Stanford University/Palo Alto VA, UC San Francisco, and the San Francisco Health Department propose to serve as

a node in NIDA's national network which generates and support randomized clinical trials of drug addiction treatment.

Role: Co-Investigator (MPI: Korthuis and Humphreys)

- 12/19-11/22 Funder: Stanford Center for Health Education ("SCHE")
 Title: Psychology of Addiction and Recovery
 Purpose: Stanford University Department of Psychiatry in partnership with SCHE and Getsmarter proposes to create an online professional education course on addiction medicine for learners around the world.
 Role: Academic Director
- 7/18-7/21 Funder: Department of Governmental Relations, Stanford Hospital/Clinics
 Title: Addiction Medicine Peer Mentor Program
 Purpose: To explore the feasibility and safety of integrating a peer mentor into the Addiction Medicine Dual Diagnosis Clinic Treatment Team
 Role: Co-Investigator (MPI: Raheemullah and Gallagher)
- 10/15-10/20 Funder: National Institute of Alcohol Abuse & Alcoholism
 Title: CNS Deficits: Interaction of Age & Alcoholism, R01 AA005965
 Purpose: Determine the impact of heavy, chronic alcohol use on brain structure and function, and the capacity of the brain to heal in a period of abstinence.
 Role: Co-Investigator (MPI: Pfefferbaum and Zahr)

Previous Funding

- 1/00-1/01 Funder: American Psychiatric Association and Eli Lilly Training Grant
 Title: Facial Emotion Processing in Patients with Bipolar Disorder
 Role: PI
- 7/01-7/02 Funder: National Institute of Mental Health Research Fellowship
 Title: Facial and Vocal Emotion Processing in Mood Disorders
 Role: PI
- 11/01-11/03 Funder: National Institute of Mental Health
 Title: Systematic Treatment Enhancement Program for Bipolar Disorder
 Role: Site-Investigator (PI: Sachs, Mass General)
- 12/08-12/10 Funder: National Institute of Mental Health
 Title: HPA Axis in Psychotic Depression, 2 RO1 MH050604-12
 Role: Co-Investigator (PI: Schatzberg)
- 10/09-10/14 Funder: National Institute on Drug Abuse

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Title: Extended Treatment for Smoking Cessation, R01 DA017441
 Role: Co-Investigator (PI: David)

- 7/11-7/14 Funder: National Institute of Health
 Title: Genetics of Symptomatology and Treatment Response in Depression
 Role: Investigator (PI: Murphy)
- 1/12-12/15 Funder: Michael Alan Rosen Foundation
 Title: Screening and Brief Intervention for Substance Misuse/Abuse
 Role: Co- PI (Co-PI: Humphreys)
- 11/13-11/14 Funder: Stanford Center at Peking University (SCPKU)
 Title: Narratives of Addiction in Contemporary China
 Role: PI
- 1/14-1/15 Funder: Peter F. McManus Charitable Trust, SPO #112718
 Title: Exploring Physician Opioid Prescribing Using a Novel Approach to Data Mining of Medical Records
 Role: PI
- 1/14-1/15 Funder: American Board of Addiction Medicine/Conrad N. Hilton Foundation
 Title: 2014 Next Generation Award for Adolescent Substance Use Prevention
 Role: PI
- 11/14-11/15 Funder: Stanford Center for Continuing Medical Education (SCCME)
 Title: Prescription Drug Abuse: Compassionate Care for a Complex Problem
 Role: PI
- 1/15-1/16 Funder: American Board of Addiction Medicine/Conrad N. Hilton Foundation
 Title: 2015 Next Generation Award for Adolescent Substance Use Prevention
 Role: PI
- 7/16-7/17 Funder: Stanford Center for Continuing Medical Education (SCCME)
 Title: Tapering Patients off of Chronic Opioid Therapy
 Role: PI
- 11/2017 Funder: VA Center for Innovation to Implementation
 Title: The Hidden Role of Benzodiazepines in the Prescription Drug Epidemic
 Role: Small grant awardee

Scholarly Work

Books

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Lembke, A. *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Johns Hopkins University Press, November 15, 2016

Peer-Reviewed Online Stanford EdX CME Courses

1. **Lembke, A.** *Prescription Drug Misuse and Addiction: Compassionate Care for a Complex Problem*: Enduring Online Course, Stanford Center for Continuing Medical Education, Stanford, California <https://www.edx.org/bio/anna-lembke>
2. **Lembke, A.** *Tapering Patients Off of Chronic Opioid Therapy*, Enduring Online Course, Stanford Center for Continuing Medical Education, Stanford, California, <https://www.edx.org/bio/anna-lembke>

Peer-Reviewed Original Research Articles

1. **Lembke A**, Ketter TA. Impaired Recognition of Facial Emotion in Mania *American Journal of Psychiatry* 2002; 159(2):302-4.
2. Menon V, Levitin DJ, Smith BK, **Lembke A**, Krasnow BD, Glazer D, Glover GH, McAdams S. Neural Correlates of Timbre Change in Harmonic Sounds *Neuroimage* 2002; 17(4):1742-54.
3. Janenawasin S, Wang PW, **Lembke A**, Schumacher M, Das B, Santosa CM, Mongkolcheep J, Ketter TA. Olanzapine in Diverse Syndromal and Subsyndromal Exacerbations of Bipolar Disorders *Bipolar Disorders* 2002; 4(5):328-34.
4. DeBattista C, **Lembke A**, Solvason HB, Ghebremichael R, Poirier J. A Prospective Trial of Modafinil as an Adjunctive Treatment of Major Depression. *Journal of Clinical Psychopharmacology* 2004; 24(1):87-90.
5. **Lembke A**, Miklowitz D, Otto M, Wisniewski S, Sachs N, Thase M, Ketter TA. Psychosocial Service Utilization by Patients with Bipolar Disorders. *Journal of Psychiatric Practice* 2004; 10(2):81-87.
6. Miklowitz, D.J., Otto, M.W., Wisniewski, S.R., Araga, M., Frank, E., Reilly-Harrington, N.A., **Lembke, A.**, Sachs, G.S. Psychotherapy, Symptom Outcomes, and Role Functioning Over One Year among Patients with Bipolar Disorder. *Psychiatric Services* 2006; 57(7):959-65.

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7. **Lembke, A.**, Bradley, K.A., Henderson, P., Moos, R. Harris, A.H.S., Alcohol Screening Scores and the Risk of New-Onset Gastrointestinal Illness or Related Hospitalization. *Journal of General Internal Medicine*, 2011; 26(7):777-782.
8. Che, A., Gomez, R., Keller, J., **Lembke, A.**, Tennakoon, L., Cohen, G., Schatzberg, A., The relationships of positive and negative symptoms with neuropsychological functioning and their ability to predict verbal memory in psychotic major depression. *Psychiatry Research*, 2012; 198(1):34-8.
9. Harris, A.H.S., **Lembke, A.**, Henderson, P., Gupta, S., Moos, R., & Bradley, K.A. Risk of Future Trauma Based on Alcohol Screening Scores: A Two-Year Prospective Cohort Study Among US Veterans. *Addiction Science & Clinical Practice*, 2012; 7(1):6.
10. **Lembke, A.**, Gomez, R., Tenakoon, L., Keller, J., Cohen, G., Williams, G. H., Kraemer, F.B., Schatzberg, A.F., The mineralocorticoid receptor agonist fludrocortisone, differentially inhibits pituitary-adrenal activity in humans with psychotic major depression. *Psychoneuroendocrinology*, 2012, 38(1):115-121.
11. Del Re, A.C., Gordon, A.K., **Lembke, A.** Harris, A.H.S., Utilization of Topiramate to Treat Alcohol Use Disorders in the Veterans Health Administration. *Addiction Science and Clinical Practice*, 2013;8(12).
12. Harris, AHS, Ellerbe, L, Reeder, RN, Bowe, T, Gordon, AJ, Hagedorn, H, Oliva, E, **Lembke, A.**, Kivlahan, D, Trafton, JA. Pharmacotherapy and Alcohol Dependence: Perceived treatment barriers and action strategies among Veterans Health Administration service providers. *Psychological Services*, 2013; 10(4):410-419.
13. Kelley, R., Garrett, A., Cohen, J., Gomez, R., **Lembke, A.**, Keller, J., Reiss, A.L., Schatzberg, A. Altered brain function underlying verbal memory encoding and retrieval in psychotic major depression. *Psychiatry Research: Neuroimaging*, 2013; 38 (1):115-121.
14. **Lembke, A.** 2013. Sacrifice, stigma, and free-riding in Alcoholics Anonymous (AA): A new perspective on behavior change in self-help organizations for addiction. In: University, S. (ed.). https://www.chapman.edu/research/institutes-and-centers/institute-religion-economics-society/_files/guest-lectures/lembke-paper.pdf.
15. Yuen KW, Garner JP, Carson DS, Keller J, **Lembke A**, Hyde SA, Kenna HA, Tennakoon L, Schatzberg AF, Parker KJ. Plasma oxytocin concentrations are lower in depressed vs. healthy control women and are independent of cortisol. *Journal of Psychiatric Research*, 2014; 51:30-6.
16. Schatzberg AF, Keller J, Tennakoon L, **Lembke A**, Williams G, Kraemer FB, Sarginson JE, Lazzeroni LC, Murphy GM. HPA axis genetic variation, cortisol and psychosis in major

- depression. *Molecular Psychiatry*, 2014; 19(2):220-7.
17. Maclean D, Gupta S, **Lembke A**, Manning CD, Heer J. Forum77: An Analysis of an Online Health Forum Dedicated to Addiction Recovery. *ACM Computer-Supported Cooperative Work (CSCW)*, <https://idl.cs.washington.edu/papers/forum77/>; 2015; *Role: Data analysis, manuscript preparation. *Best Paper Honorable Mention.*
 18. **Lembke, A.**, Cheng, Niushen. A Qualitative Study of Treatment-Seeking Heroin Users in Contemporary China, *Addiction Science and Clinical Practice*, 2015;10:23.
 19. Chen, J., Humphreys, K., Shah, N.H., **Lembke, A.**. Distribution of Opioids by Different Types of Medicare Prescribers, *JAMA Internal Medicine*, 2016; 176(2):259-261.
 20. Haug, N.A., Bielenberg, J., Linder, S. H., **Lembke, A.**. Assessment of provider attitudes toward #naloxone on Twitter. *Substance Abuse*, 2016; 37(1):35-41.
 21. **Lembke, A.**, Chen, J. Use of Opioid Agonist Therapy for Medicare Patients in 2013. *JAMA Psychiatry*, 2016;73(9):990-992. doi:10.1001/jamapsychiatry.2016.1390
 22. Keller, J., Gomez, R., Williams, G., **Lembke, A.**, Lazzeroni, L., Murphy, G.M. Jr, Schatzberg, A.F. HPA Axis in Major Depression: Cortisol, Clinical Symptomatology, and Genetic Variation Predict Cognition, *Molecular Psychiatry*, Feb; 19(2): 220–227. doi: 10.1038/mp.2016.120 2016. *Role: Study physician, manuscript preparation.*
 23. Stein, M., Kanabar, M., Anderson, B.J., **Lembke, A.**, Bailey, G.L. Reasons for Benzodiazepine Use Among Persons Seeking Opioid Detoxification, *Journal of Substance Abuse Treatment*, 2016; September; 68: 57–61. *Role: Data analysis, manuscript preparation.*
 24. Leyro, T. M., Crew, E. E., Bryson, S. W., **Lembke, A.**, Bailey, S. R., Prochaska, J. J., Henriksen, L., Fortmann, S. P., Killen, J. D., Killen, D. T., Hall, S. M., David, S. P. Retrospective analysis of changing characteristics of treatment-seeking smokers: implications for further reducing smoking prevalence. *BMJ* 2016; 6 (6). *Role: Study physician, manuscript preparation.*
 25. Laude, J. R., Bailey, S. R., Crew, E., Varady, A., **Lembke, A.**, McFall, D., David, S. P. (2017). Extended treatment for cigarette smoking cessation: A randomized control trial. *Addiction*. <https://doi.org/10.1111/add.13806> *Role: Study physician, manuscript preparation.*
 26. Raber, I., Ball, A., Papac, J., Aggarwal, A., Sussman, R., Basaviah, P., Newmark, J. **Lembke, A.** Qualitative Assessment of Clerkship Students' Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum, *Academic Psychiatry*, 2018;42:664, doi:

10.1007/s40596-018-0927-1

27. Azad, **Lembke, A.** et al, Patterns of Opioid and Benzodiazepine Use in Opioid-Naïve Patients with Newly Diagnosed Low Back and Lower Extremity Pain, *Journal of General Internal Medicine*, 2020, 35(1):291-297. doi: 10.1007/s11606-019-05549-8. *Role: Data interpretation, manuscript preparation*
28. Haug, N. A., Morimoto, E. E., **Lembke, A.** Online mutual-help intervention for reducing heavy alcohol use. *Journal of Addictive Diseases*, 2020. <https://doi.org/10.1080/10550887.2020.1747331>

Published Peer-Reviewed Perspectives, Case Reports, and Reviews

1. **Lembke A.** A Piece of My Mind: "A letter from the foreign legion" *JAMA*, 1996; 276(21):1704.
2. Crowley RS, **Lembke A**, Horouptian DS. Isolated Meningeal Vasculopathy Associated with Clostridium Septicum Infection *Neurology* 1997; 48(1):265-7.
3. Barry JJ, Huynh N, **Lembke A.** Depression in Individuals with Epilepsy *Current Treatment Options in Neurology*, 2000; 2(6):571-585.
4. **Lembke A.** "Mind" and "Brain" *American Journal of Psychiatry*, 2001; 158(11):1939-1940.
5. DeBattista C, Trivedi M, Kern J, **Lembke A.** The Status of Evidence-Based Guidelines and Algorithms in the Treatment of Depression *Psychiatric Annals*, 2002; 32(11):658-663.
6. Sommer B, Fenn H, P. P, DeBattista C, **Lembke A**, Wang P, Flores B. Safety of Antidepressants in the Elderly. *Expert Opinion on Drug Safety*, 2003; 2(4):367-383.
7. **Lembke A.** A Friday in the Life of an Academic Psychiatrist *Academic Psychiatry*, 2003; 27(3):214-215.
8. Barry J.J., **Lembke A.**, Bullock K.D. Current Status of the Utilization of Antiepileptic Treatments in Mood, Anxiety and Aggression: Drugs and devices. *Clinical EEG and Neuroscience*, 2004; 35(1):4-13.
9. **Lembke, A.** Why is this Special Issue on Women's Professional Development in Psychiatry Necessary? *Academic Psychiatry*, 2004 28(4):275-277.
10. Debattista, C., **Lembke, A.**, Update on Augmentation of Antidepressant Response in Resistant Depression. *Current Psychiatry Report*, 2005; 7(6):435-40.

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11. **Lembke A**, Johnson K, DeBattista C. Depression and Smoking Cessation: Does the Evidence Support Psychiatric Practice? *Neuropsychiatric Disease and Treatment*, 2007; 3(4):1-7.
12. DeBattista, C, **Lembke, A**. Psychotic Major Depression: Phenomenology and the Pursuit of Optimal Treatment. *Primary Psychiatry*, 2008; 15(4):59-64.
13. Schatzberg, A.F., Solvason, H.B., Keller, J., **Lembke, A**. Antidepressant Interventions in the HPA system. *Journal of Affective Disorders*, 2008; 107(Suppl.1):S40-S41.
14. **Lembke, A**. Depressed Smokers: A Guide to Treatment Based on the Evidence. *Depression: Mind and Body*, 2009;4(3):96-101.
15. **Lembke, A**. Optimal Dosing of Lithium, Valproic Acid, and Lamotrigine in the Treatment of Mood Disorders. *Primary Psychiatry*, 2009; 16(10):33-38.
16. **Lembke, A.**, Humphreys, K., Moderation Management: A Mutual-Help Organization for Problem Drinkers who are not Alcohol Dependent. *Journal of Groups in Addiction and Recovery*, 2012; 7(2-4):130-141.
17. **Lembke, A**. Time to Abandon the Self-Medication Hypothesis in Patients with Psychiatric Disorders. *The American Journal of Drug and Alcohol Abuse*, 2012, 38(6):524-529.
18. **Lembke, A**. Why doctors prescribe opioids to known opioid abusers. *New England Journal of Medicine*. October 25, 2012; 367(17):1580-1581
19. **Lembke, A**. From Self-Medication to Intoxication: Time for a Paradigm Shift. *Addiction*, 2013; 108(4):670-671.
20. Humphreys, K., **Lembke, A**. Recovery oriented policies and care systems in the U.K. and the USA. *Drug and Alcohol Review*, 2014; 33 (1):13-18.
21. **Lembke, A**, Humphreys, K. A Call to Include People with Mental Illness and Substance Use Disorders Alongside ‘Regular’ Smokers in Smoking Cessation Research, *Tobacco Control*, 2015;25(3):261-2.
22. **Lembke, A.**, Humphreys, K., Newmark, J. Weighing the Risks and Benefits of Chronic Opioid Therapy, *American Family Physician*, 2016; 93(12):982-990.
23. Ogbonna, C., **Lembke, A**. Tapering Patients Off of Benzodiazepines, *American Family Physician*, 2017 Nov 1;96(9):606-608.

24. Prekupec, M.P., Sussman, R.S., Sher, Y., **Lembke, A.** Relapse on ketamine followed by severe and prolonged withdrawal: A cautionary case and review of potential medical therapies. *J Nat Sci*, 3(10):e450, 2017.
25. **Lembke, A.** The Opioid Epidemic is a Symptom of our Faltering Health Care System, *The British Medical Journal*, published online October 30, 2017
<http://blogs.bmj.com/bmj/2017/10/31/anna-lembke-the-opioid-epidemic-is-a-symptom-of-our-faltering-healthcare-system/>
26. **Lembke, A.** Why Addiction Should Be Considered a Disease, *Judges' Journal*, 2018 Jan; Volume: 57 Issue: 1
27. **Lembke, A.**, Papac, J., Humphreys, K. Our Other Prescription Drug Problem, *NEJM*, 2018; 378(8):693-695.
28. **Lembke, A.**, Humphreys, K. The Opioid Epidemic as a Watershed Moment for Physician Training in Addiction Medicine, *Academic Psychiatry*, 2018; 42(2):269-272.
29. Harrison, T. K., Kornfeld, H., Aggarwal, A. K., & **Lembke, A.** Perioperative Considerations for the Patient with Opioid Use Disorder on Buprenorphine, Methadone, or Naltrexone Maintenance Therapy. *Anesthesiology Clinics*, 2018; 36(3), 345–359.
<https://doi.org/10.1016/j.anclin.2018.04.002>
30. **Lembke, A.** Ottestad, E., Schmiesing, C. Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period, *Pain Medicine*, 2019; 20(3):425-428. <https://doi.org/10.1093/pmy019>
31. Raheemullah, A., **Lembke, A.** Initiating Opioid Agonist Treatment for Opioid Use Disorder in the Inpatient Setting: A Teachable Moment, *JAMA Internal Medicine*, 2019; 179(3):427-428.
32. Chou, R., Ballantyne, J., **Lembke, A.**, Rethinking Opioid Dose Tapering, Prescription Opioid Dependence, and Indications for Buprenorphine, *Annals of Internal Medicine*, 2019; doi:10.7326/M19-1488
33. **Lembke, A.**, Tapering Long Term Opioid Therapy, *American Family Physician*, Volume 101, Number 1, January 1, 2020
34. Raheemullah, A., **Lembke, A.** Buprenorphine Induction Without Opioid Withdrawal: A Case Series of 15 Opioid-Dependent Inpatients Induced on Buprenorphine Using Microdoses of Transdermal Buprenorphine. *American Journal of Therapeutics*, 2019.

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1. Barry JJ, **Lembke A**, Huynh N: Affective Disorders in Epilepsy, in *Psychiatric Issues in Epilepsy: A Practical Guide to Diagnosis and Treatment*. Edited by Ettinger AB, Kanner AM. Philadelphia, Lippincott Williams and Wilkins, 2001, pp 45-72
2. Ketter T, Wang P, Dieckmann N, **Lembke A**, Becker O, Camilleri C: Brain Anatomic Circuits and the Pathophysiology of Affective Disorders, in *Brain Imaging in Affective Disorders*. Edited by Soares J. New York, Marcel Dekker, Inc., 2002, pp 79-118
3. Ketter T, Wang P, **Lembke A**, Sachs N: Physiological and Pharmacological Induction of Affect, in *The Handbook of Affective Science*. Edited by RJ D, KR S, HH G. New York, Oxford University Press, 2002, pp 930-962
4. Constantino MJ, **Lembke A**, Fischer C, Arnow BA: Adult Depression: Characteristics, Burdens, Models, and Interventions, in *Mental Disorders of the New Millennium, vol 1: Behavioral Issues*. Edited by Plante RG, Praeger Publishers, 2006, pp. 139-166
5. Barry JJ, **Lembke A**, Gisbert PA, Gilliam F. Affective Disorders in Epilepsy, in *Psychiatric Issues in Epilepsy*. Edited by Ettinger AB, Kanner AM. Philadelphia, Lippincott Williams & Wilkins, 2007, pp 203-247
6. **Lembke A**, DeBattista C. Review of a Randomized-Controlled Trial of Adjunctive Bupropion in the Treatment of SSRI-Induced Sexual Dysfunction, in *Progress in Neurotherapeutics and Neuropsychopharmacology*, vol 2. Edited by Cummings JL, Cambridge University Press, 2007, pp 187-192
7. **Lembke, A**, Humphreys, K. Alcoholics Anonymous, in *Encyclopedia of Drugs, Alcohol & Addictive Behavior*, 3rd Edition. Edited by Korsmeyer P and Kranzler H, Macmillan Reference USA, 2008, pg. 122
8. Cohen, G., **Lembke, A**. Childhood Behavior and Later Substance Use, in *Encyclopedia of Drugs, Alcohol & Addictive Behavior*, 3rd Edition. Edited by Korsmeyer P and Kranzler H, Macmillan Reference USA, 2008
9. **Lembke A**, Humphreys K. Chapter 26: Substance Use Disorder Presenting as a Mood Disorder in *How To Practice Evidence Based Psychiatry: Basic Principles and Case Studies*. Edited by Taylor CB, APPI, Washington, D.C., 2009 , pp 233-246
10. **Lembke, A.**, Humphreys, K. Moos, R. Diagnosis, Development, and Treatment of Substance Use Disorders among Adolescents and Young Adults, in *Stanford School of Medicine Handbook of Developmental Psychiatry*. Edited by Steiner, H, NY, Jossey/Bass/Wiley, 2010, pp. 365-396

11. **Lembke, A.**, & Humphreys, K. What self-help organizations tell us about the syndrome model of addiction. In Shaffer HJ (Editor-in-Chief), LaPlante DA and Nelson SA (Associate Editors), *APA Addiction Syndrome Handbook: Vol. 2. Recovery, Prevention, and other Issues*, Washington, DC: American Psychological Association, 2012, pp. 157–168
12. **Lembke, A.**, Stanford, M. Clinical Management of Alcohol Use Disorders in the Neurology Clinic, Handbook of Clinical Neurology, Vol 125, 3rd Series, *Alcohol and the Nervous System* 1E, Edited by Sullivan, EV Pfefferbaum, A, Elsevier, 2014
13. Hall R, **Lembke A.** Substance Use Disorders in Adolescence. In: Steiner H (Ed) with Hall R. *Treating Adolescents* (2nd Edition). Westford, Massachusetts: Wiley, 2015, pp 141-164
14. **Lembke, A.**, Alcoholism and drug abuse, sociology of. In S. Martin (Ed.), *The SAGE encyclopedia of alcohol: Social, cultural, and historical perspectives*. (Vol. 1, pp. 98-104). Thousand Oaks, CA: SAGE Publications, Inc. 2015 doi: <http://dx.doi.org/10.4135/9781483331096.n27>
15. **Lembke, A.**, Moderation management. In S. Martin (Ed.), *The SAGE encyclopedia of alcohol: Social, cultural, and historical perspectives*. (Vol. 13, pp. 872-874). Thousand Oaks, CA: SAGE Publications, Inc. 2015 doi: <http://dx.doi.org/10.4135/9781483331096.n334>
16. **Lembke, A.**, Humphreys, K. Self-Help Organizations for Substance Use Disorders, in *Oxford Handbook on Substance Use Disorders*, Edited by Sher, KJ, Oxford University Press, 2016
17. Ogbonna C, **Lembke A.** Alcohol and substance use and co-occurring behaviors. In Roberts LW (editor). University Student Mental Health: A Guide for Psychiatrist, Psychologists, and Leaders Serving in Higher Education. Arlington, VA: American Psychiatric Publishing, Inc., 2018.
18. **Lembke, A.**, Raheemullah, A. Addiction and Exercise. In Noordsy DL, (editor). *Lifestyle Psychiatry: Using Exercise, Diet and Mindfulness to Manage Psychiatric Disorders*. Washington DC: American Psychiatric Publishing. (2019)\

Other Publications

1. **Lembke, A.** A Psychosocial Approach to Postpartum Depression *Psychiatric Times* 2002; XIX(6):11

2. **Lembke, A.** A downside of electronic health records: How 90 percent of Merced County, California patients became Albanian, *Scope*, the Stanford University School of Medicine blog, October 11, 2012.
3. **Lembke, A.** To reduce use, educate teens on the risks of marijuana and prescription drugs, *Scope*, the Stanford University School of Medicine blog, October 18, 2012.
4. **Lembke, A.** Why doctors prescribe opioids to patients they know are abusing them, *Scope*, the Stanford University School of Medicine blog, October 25, 2012.
5. **Lembke, A.** How to make alcoholics in recovery feel welcome this holiday season, *Scope*, the Stanford University School of Medicine blog, December 10, 2012.
6. **Lembke, A.** The DSM-V Gets it Right. *The Fix*, April 11, 2013.
7. **Lembke, A.** Inside the Mind of an Addiction Medicine Physician, *The Fix*, December 4, 2014.
8. **Lembke, A.** Unmet Expectations: Testifying before Congress on the Opioid Abuse Epidemic, *Scope*, the Stanford University School of Medicine blog, April 29, 2015
9. **Lembke, A.** Ask an Expert. Should I go off Suboxone? If so, how? *The Fix*, April 29, 2015
10. **Lembke, A.** Ask an Expert: Should I Go Through Detox if I'm Not Sure I Want to Be Abstinent? *The Fix*, May 10, 2016
11. **Lembke, A.** Prince, opioids and the rest of us: America needs a massive public education campaign to help people hooked on Percocet and related drugs, *New York Daily News Op-Ed*, May 11, 2016
12. **Lembke, A.** Be sure the check the PDMP before prescribing controlled medications, *Psychiatric News*, June 17, 2016
<http://psychnews.psychiatryonline.org/doi/full/10.1176/appi.pn.2016.pp6b2>
13. **Lembke, A.** The Compassionate Doctor, the Narcissistic Injury, and the Prescription Opioid Epidemic. *The Fix*, Nov 30, 2016 <https://www.thefix.com/compassionate-doctor-narcissistic-injury-and-prescription-opioid-epidemic>
14. **Lembke, A.** Commentary provided in response to Joseph Bernstein's "Not the Last Word: Viscosupplementation, Opioid Overuse, and the Excesses of Empathy", *Clin Orthop Relat Res* (2017) 475:2369–2372

15. **Lembke, A.** Purdue Pharma is Done Promoting Opioids: Here's Why It's a Big Deal, *Fortune Magazine*, Feb 2018 <http://fortune.com/2018/02/13/purdue-pharma-oxycontin-opioid-crisis/>
16. **Lembke A.** Can medical marijuana replace opioids to relieve cancer pain? HemOnc Today. 2018;19(24):13.

Selected Invited Lectures/Testimony (last 5 years)

Regional Audience

1. Feb 2015 *Drug Addiction and the Internet: Justin's Story*, Psychiatry Grand Rounds, Alta Bates Summit Medical Center, Berkeley, CA
2. Feb 2015 *Pain, Addiction, and the Drug-Seeking Patient: Compassionate Care for a Complex Problem*, Santa Clara Valley Medical Center CME Symposium on Addiction, Santa Clara, CA
3. Mar 2015 *The Prescription Drug Epidemic: Technology as Both Friend and Foe*, Northern California Psychiatric Society Annual CME Conference, Monterey, CA
4. Sept 2015 *The Prescription Drug Epidemic: Preserving Compassion for the Drug-Seeking Patient*, Mills Peninsula Health Services CME Lecture Series, San Mateo, CA
5. Oct 2015 *Addiction Medicine: Managing Prescription Drug Misuse and Addiction, Emerging and Innovative Trends in Psychiatry and Behavioral Health*, Stanford University School of Medicine, Stanford, CA
6. Oct 2015 *The Prescription Drug Epidemic: How Doctors are Complicit, and How We Can Do Better*, Regional Medical Center of San Jose CME Lecture Series, San Jose, CA
7. Dec 2015 *Exploring Dual Diagnosis: What came first, the substance use disorder or the psychiatric disorder, and does it even matter?* Mills Peninsula Health Services CME Lecture Series, San Mateo, CA
8. Jan 2016 *The Prescription Drug Epidemic and the Doctor Patient Relationship*, San Francisco General Hospital Primary Care Grand Rounds, San Francisco, CA
9. Mar 2016 *Protecting our Developing Youth: Adolescent Addiction, Prevention and Recovery*, Keynote Speaker, Adolescent Counseling Services, East Palo Alto, CA
10. Mar 2016 *Opioid Therapy for Chronic Non-Cancer Pain*, 2016 Third Annual Addiction Medicine Conference, San Jose Valley Medical Center, San Jose, CA

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11. Mar 2016 *The Prescription Drug Epidemic*, Keynote Speaker, Stanford Annual Adjunct Faculty Retreat, Palo Alto, CA
12. Sept 2016 *Pharmacotherapy for Substance Use Disorders*, Department of Psychiatry Annual CME Conference, Stanford University School of Medicine, Stanford, CA
13. Nov 2016 *Prescription Drug Misuse and the Doctor Patient Relationship*, Psychiatry, San Mateo County Health Systems Grand Rounds, San Mateo, CA
14. Mar 2017 *The Worst Opioid Epidemic in U.S. History: How did we get here, and how can we get out?* Santa Cruz Health Care Initiative, Santa Cruz, CA
15. Mar 2017 *The Canary in the Coal Mine: The Prescription Drug Epidemic as a Symptom of a Faltering Health Care System* Valley Care Medical, Pleasanton, CA
16. Mar 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Northern California Psychiatric Society, Napa Valley, CA
17. Apr 2017 *Pharmacotherapy for Addictive Disorders*, Alta Bates Grand Rounds, Alta Bates Hospital Berkeley, CA
18. May 2017 *The Worst Opioid Epidemic in U.S. History: How did we get here, and how can we get out?* Stanford Health Matters, Stanford, CA
19. May 2017 *The Compassionate Doctor, the Suffering Patient, and the Prescription Drug Epidemic*, Central California Alliance for Health (the Alliance), Merced, California
20. May 2017 *The Compassionate Doctor, the Suffering Patient, and the Prescription Drug Epidemic*, Janus of Santa Cruz, Seaside, California
21. June 2017 *Overprescribing in the Elderly: Causes, Risks, and Interventions*, Keynote Speaker at the 17th Annual California Senior Injury Prevention Educational Forum, Oakland, CA
22. Feb 2018 *Is Marijuana a Harm Reduction Strategy?*, Stanford Psychiatry Grand Rounds, Stanford University School of Medicine, Stanford, CA
23. Mar 2018 *Raising T(w)eens in a Dopamine Saturated World*, Woodside Priory High School, Woodside, CA
24. Mar 2018 *Raising T(w)eens in a Dopamine Saturated World*, Sacred Heart High School, Menlo Park, CA

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25. Apr 2018 *The Opioid Epidemic: What Doctors and Hospitals Can Do*, California Pacific Medical Center Internal Medicine Grand Rounds, San Francisco, CA
26. Apr 2018 *Adolescent Substance Abuse: Risk, Resilience, Prevention, and Treatment*, 2018 Adolescent Mental Wellness Conference, sponsored by Stanford University, Santa Clara, CA
27. Jul 2018 *Understanding the Opioid Crisis at the End of Life*, San Francisco Bay Area Hospice and Palliative Nurses Association, Stanford, CA
28. Aug 2018 *The Opioid Epidemic: How We Got Here, and How to Get Out*, Apple Corporation, Cupertino, CA
29. Oct 2018 *The Pleasure Pain Balance*, Los Altos High School “STEAM Week”, Los Altos, CA
30. Jan 2019 *From Freud to Fentanyl: The Opioid Epidemic as a Symptom of a Faltering Health Care System*, Internal Medicine Grand Rounds, Santa Clara Valley Medical Center, Santa Clara, CA
31. Feb 2019 *Our Other Prescription Drug Problem (Benzodiazepines and How to Taper)*, Internal Medicine Grand Rounds, San Mateo Medical Center, San Mateo, CA
32. Jul 2019 *Social Media and Device Addiction*, 27th Annual Pediatric Update, Stanford University School of Medicine, Stanford, DA
33. Aug 2019 *Medical Cannabis: Clinical Issues*, 8th Annual Navigating Spine Conference, Stanford University School of Medicine, Stanford, CA
34. June 2020, *From Freud to Fentanyl: The Opioid Epidemic as a Symptom of our Faltering Health Care System*, Alta Bates Grand Rounds, Berkeley, CA
35. Aug 2020 *Medical Cannabis: Clinical Issues*, 8th Annual Navigating Spine Conference, Stanford University School of Medicine, Stanford, CA

National/International Audience

1. Sept 2015 *The Prescription Drug Epidemic: Compassionate Care for a Complex Problem*, Psychiatry Grand Rounds Speaker, Oregon Health Sciences University, Portland, CA
2. Oct 2015 *Chronic Pain and Addiction: The Compassionate Doctor, The Narcissistic Injury, and the Primitive Defense*, California Society of Addiction Medicine, State of the Art Annual Conference, San Francisco, CA

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3. Oct 2015 *Prescription Drug Misuse and the Doctor Patient Relationship*, Keynote Speaker, American Correctional Healthcare Services Association, Tailoring Health Care for Inmates, Sacramento, CA
4. Mar 2016 *Chronic Opioids: Shifting the Paradigm*, Keynote Speaker, Samaritan Center & Health Career and Training Center, Lebanon, OR
5. Jun 2016 *The Compassionate Doctor, the Drug Seeking Patient, the Narcissistic Injury, and the Primitive Defense*, Keynote Speaker, Cedar Sinai Annual Psychiatric Conference, Los Angeles, CA
6. Sept 2016 *Myths and Facts about Opioids*, DCRx: The DC Center for Rational Prescribing; <http://doh.dc.gov/dcrx>, Washington, DC
7. Sept 2016 *Getting Patients Off of Opioids*, DCRx: The DC Center for Rational Prescribing; <http://doh.dc.gov/dcrx>, Washington, DC
8. Oct 2016 *State of the Art Treatment for Substance Use Disorders and other Addictions*, Keynote Speaker, 3-part lecture series, Beijing University, #6 Hospital, Beijing, China
9. Jan 2017 *Effective Strategies for the Non-Adherent Buprenorphine Patient: Rational Monitoring and Contingency*, California Society of Addiction Medicine, Treating Addiction in the Primary Care Safety Net, Webinar
10. Feb 2017 *How to safely taper patients off high dose prescription opioids for chronic pain*, Keynote Speaker, California Center for Care Innovations, Treating Addiction in the Primary Care Safety Net, Los Angeles, CA
11. Feb 2017 *The Worst Opioid Epidemic in U.S. History: How did we get here, and how can we get out?* Stanford Parents Weekend Back to School, Stanford, CA
12. Feb 2017 *When Pain Treatment Becomes Addiction Treatment*, American Psychological Association Annual Meeting, San Francisco, CA
13. Feb 2017 *Parallel Crises: The Over and Under Prescription of Opioids*, American Association of Medical Colleges (AAMC) Webinar
14. Mar 2017 *How Doctors Contributed to the Opioid Epidemic, and What We Can Do to Fix It*, Intermountain Health Care Book Club Speaker for *Drug Dealer, MD*, Intermountain Health Care, Salt Lake City, UT

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15. Mar 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Culture and Politics of Mental Health, Anthropology 1737-1020, Professor Tomas Matza, University of Pittsburgh, Pittsburgh, PA
16. Apr 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Stanford TEDx, Stanford, CA
17. Apr 2017 Invited speaker, 6th Annual Health Technology Forum Innovation Conference: *Common Good!* Stanford University School of Medicine, Stanford, CA
18. Apr 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Keynote Speaker, 8th Annual Lloyd C. Elam Symposium, Meharry Medical College, Nashville, TN
19. Apr 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Keynote Speaker, Association of Contextual Behavioral Sciences (ACBS), Chicago, IL
20. May 2017 *Invisible Forces Driving the Opioid Epidemic: From Disability Reform to Illness Narratives*, Keynote Speaker, OPG 6th Annual Pain Conference Agenda, Ashland, OR
21. May 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Internal Medicine Residency Program Invited Visiting Professor and Grand Rounds Speaker, Johns Hopkins Bayview Medical Center, Baltimore, MD
22. June 2017 *Invisible Forces Driving the Opioid Epidemic: From Disability Reform to Illness Narratives*, Keynote Speaker, PharmedOut Annual Conference, Georgetown University Medical Center, Washington, DC
23. Sept 2017 *The Opioid Epidemic*, Keynote Speaker, Department of Labor West Coast Symposium, San Francisco, CA
24. Sept 2017 *Treating Addiction without Feeding It*, Keynote Speaker, American Correctional Health Services Association (ACHSA) "Modern Challenges in Jails and Prisons", San Jose, CA
25. Sept 2017 *Invisible Forces Driving the Prescription Drug Epidemic: From Disability Reform to Illness Narratives*, Keynote Speaker, The International Benzodiazepine Symposium, Redmond, OR
26. Sept 2017 *Reframing Medical Practice Involving Controlled Substances*, Keynote Speaker, The Association of State and Territorial Health Officials (ASTHO) 2017 Annual Conference, Washington, DC

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27. Oct 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Keynote Speaker, The Patient Safety Institute for Mission Health 3rd Annual National Patient Safety Conference – Cultivating a Culture of Safety, Asheville, NC
28. Nov 2017 *The Opioid Epidemic, How We Got Here, and How We Can Get Out*, Keynote Speaker, American Association of Medical Colleges, Learn, Serve, Lead, Boston, MA
29. Nov 2017 *The Opioid Fallout: Lives, Jobs and a Lost Generation*, Bloomberg News Live, The Year Ahead, Bloomberg Headquarters, New York City, NY
30. Nov 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Grand Rounds Speaker, Westchester Medical Center, Westchester, NY
31. Dec 2017 *The Opioid Epidemic: How We Got Here, and How We Can Get Out*, Keynote Speaker, Primary Care and Behavioral Health Integration Summit, Health Quality Partners, San Diego, CA
32. Jan 2018 *How to Survive in a Dopamine Saturated World*, Psychiatry Grand Rounds, Vanderbilt University School of Medicine, Nashville, TN
33. April 2018 *Drug Dealer, MD*, Keynote Speaker, STAR Trauma Recovery Center, Ohio State University Medical School, Columbus, OH
34. May 2018 *The Opioid Epidemic: What Doctors and Hospitals Can Do*, Alpha Omega Alpha Visiting Professorship, Psychiatry Grand Rounds, University of Kansas School of Medicine, Kansas City, KS
35. May 2018 *Opioids, Pain and Addiction Treatment: Pioneering Change*, Oregon Pain Guidance Annual Conference, Eugene, OR
36. June 2018 *The Opioid Epidemic, How We Got Here and How to Get Out*, Indiana Prosecuting Attorneys Council (IPAC), invited speaker, French Lick, IN
37. June 2018 *What is Addiction and How to Treat It*, Perrin's Opioid Litigation Conference, Dallas, TX
38. Aug 2018 Moderator, *Beyond Nature and Nurture – Social Determinants of Addiction and Health*, California Society of Addiction Medicine State of the Art Annual Conference, San Francisco, CA
39. Aug 2018 *Drug Dealer, MD: The Opioid Crisis*, Apple Corporation Wellness Outreach, Cupertino, CA

40. Sept. 2018 *The Opioid Epidemic: How We Got Here, and How to Get Out*, Public Funds Forum, Laguna Beach, CA
41. Sept 2018 *Drug Dealer, MD: The Opioid Crisis*, Baton Rouge Health District Community Service Talk and Medical Center Grand Rounds, Baton Rouge, LA
42. Sept 2018 *Drug Dealer, MD: The Opioid Crisis*, Montrose Annual CME Conference, Montrose, CO
43. Oct 2018 *The Opioid Epidemic: From Freud to Fentanyl*, Keynote Speaker, PerformRX Pharmacy Benefits Manager Annual Conference, Orlando, FL
44. Oct 2018 *The Opioid Epidemic: How We Got Here, Where We Are Now, and How to Get Out*, Keynote Speaker, Distinguished Lecture Series, Annual Meeting of the American Academy of Psychiatry and the Law (AAPL), Austin, TX
45. Oct 2018 *Drug Dealer MD: The Opioid Epidemic*, Keynote Speaker, Psych Congress, Orlando, FL
46. Dec 2018 *How to Taper Patients Off of Chronic Opioid Therapy*: 69th Annual Refresher Course for Family Physicians, Montreal, Canada
47. Feb 2019 *The Opioid Epidemic: How We Got Here, Where We Are Now, and How to Get Out*, National Keynote Speaker, Ohio State University Inter-Professional Summit, Columbus, OH
48. Feb 2019 *The Opioid Epidemic: How We Got Here, Where We Are Now, and How to Get Out*, Keynote Speaker, Pain and Addiction Summit, AT&T Conference Center/University of Texas, Austin, TX
49. April 2019 *The Opioid Epidemic: From Freud to Fentanyl*, Keynote, Speaker, Geminus Community Partners Annual Conference, Merrillville, IN
50. April 2019 Invited commentator on *Deaths of Despair* for honorees Princeton Economists Ann Case and Angus Deaton, The 2019 Tanner Lectures on Human Values, Sponsored by the Office of the President and the McCoy Family Center for Ethics in Society, Stanford, CA
51. April 2019 *The Opioid Epidemic: Where We Are Now*, Keynote speaker for the National Council on Alcoholism and Drug Abuse (NCADA) Spring Awards Luncheon, St. Louis, MO
52. May 2019 *The Opioid Epidemic: Where We Are Now*, Faculty presenter Stanford Sierra Camp Womens' Alumni Wellness Retreat, Fallen Leaf Lake, CA

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- 53. May 2019 *The Opioid Epidemic: From Freud to Fentanyl*, The American Psychiatric Association Annual Meeting, San Francisco, CA
- 54. July 2019 *Rethinking Opioid Tapers, Buprenorphine Induction, and Perioperative Buprenorphine*, Opioid Response Network Texas Grand Rounds National Webinar Series
- 55. July 2019 *Tapering Guidance for Opioids*, National Academy of Medicine webinar
<https://nam.edu/event/webinar-tapering-guidance-for-opioids-existing-best-practices-and-evidence-standards/> ; <https://nam.edu/wp-content/uploads/2019/08/Tapering-webinar-two-pager-FINAL.pdf>.
- 56. November 2019 *Tapering Opioids: Compassionate Care or Punitive Policy*, AMERSA Conference, Boston, MA
- 57. December 2019 *From Freud to Fentanyl: The Opioid Epidemic as a Symptom of our Faltering Health Care System*, Southwestern Gynecologic Assembly 54th Annual Meeting: Patient and Provider at Their Best: Caring for Patients and Yourself, Dallas, TX
- 58. March 2020 *Dismantling the Addiction Industrial Complex*, 13th Annual Haas Healthcare Conference, “Foresight is 2020,” San Francisco, CA

United States Government Testimony/White House Appearances/Consulting

- 1. Apr 2015 Expert testimony for the Congress of the United States, House of Representatives, Committee on Energy and Commerce, Subcommittee on Oversight and Investigations hearing entitled “Combatting the Opioid Abuse Epidemic: Professional and Academic Perspectives,” Washington, D.C. <https://democrats-energycommerce.house.gov/committee-activity/hearings/hearing-on-combatting-the-opioid-abuse-epidemic-professional-and>
- 2. Sept 2015 Expert testimony for the White House Symposium, “Medicine Responds to the Need for Addiction Expertise”, The Office of National Drug Control Policy, The White House, Washington, D.C. <https://obamawhitehouse.archives.gov/the-press-office/2015/09/18/white-house-drug-policy-office-hosts-%E2%80%9Cmedicine-responds-addiction%E2%80%9D>
- 3. Sept 2016 Expert testimony for the United States Senate, Committee of Homeland Security and Government Affairs, Permanent Subcommittee on Investigations, on the overuse and overprescribing of prescription opioids, “Combatting the Opioid Epidemic: A Review of Anti-Abuse Efforts by Federal Authorities and Private Insurers”, Washington, D.C.
- 4. Oct 2016 Expert testimony for the White House Symposium, “Academic Medical Centers as Centers of Excellence in Addiction Medicine”, The Office of National Drug Control

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Policy, The White House, Washington, D.C. <http://www.abms.org/news-events/white-house-symposium-briefing-session-on-addiction/>

5. May 2017 Provided consultation on curbing the opioid epidemic to Nevada's Office of the Governor
6. May 2017 Provided consultation on curbing the opioid epidemic to Kentucky's Office of the Governor
7. Sept 2017 Expert Spoken and Written Testimony for the Congress of the United States, House of Representatives, "Addiction Medicine: The Urgent Need for Trained Physicians", hosted by The Addiction Medicine Foundation and co-sponsored by the Congressional Prescription Drug Abuse Caucus, the Congressional Addiction Treatment and Recovery Caucus, and the Congressional Bipartisan Heroin Task Force <https://www.youtube.com/watch?v=y6kBoQckmHw>
8. Jan 2018 Expert testimony in federal court, Judge Dan Polster presiding, in the multi-district litigation lawsuit against opioid manufacturers and distributors <https://www.law360.com/articles/1008010/inside-the-opioid-mdl-s-big-closed-door-hearing>
9. March 20, 2019 Testimony by Stanford University Professor Anna Lembke to Joint Hearing of Senate and General Assembly Health and Human Services Committees on "Opioids, cannabis, and vaping: Using science to protect public health" State of Rhode Island

Medical Expert Witness (last 5 years)

1. People v. Ingram, Philip Morris (Sup. Ct. of CA, Docket 62-144622), (2018)
2. Federal (MDL) and state (California, New York, Texas, West Virginia, Washington) litigation against opioid manufacturers, distributors, and other defendants (plaintiff side) (Jan 2018 ongoing)

Media Appearances (last 5 years)

1. Apr 2015 *Public Radio International-To the Point*, hosted by Warren Olney, prescription opioid and heroin abuse in America, invited expert.
2. Oct 2015 *OnPoint, National Public Radio*, the prescription opioid epidemic, invited expert
3. Mar 2016 *Al Jazeera* live programming, the new CDC guidelines on opioid prescribing, invited expert

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4. Mar 2016 *KCBS Radio*, San Francisco, the new CDC guidelines on opioid prescribing, invited expert
5. Apr 2016 *The Today Show* on NBC, NY, New York, appearance with Mehmet Oz discussing “The Opioid Epidemic”
6. May 2016 *KCBS Radio*, San Francisco, the FDA approves Probuphine, a buprenorphine implant, invited expert
7. Oct 2016 *Opioids: Last Week Tonight with John Oliver* (HBO),
<https://www.youtube.com/watch?v=5pdPrQFjo2o>
8. Nov 2016 *Sirius XM Radio*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
9. Nov 2016 *Wisconsin Public Radio's "Central Time" Show*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
<http://www.wpr.org/connection-between-illicit-drugs-and-doctors>
10. Nov 2016 *The Healthcare Policy Podcast with David Intocaso*, invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <http://www.stitcher.com/podcast/david-intocaso-2/the-healthcare-policy-podcast/e/what-explains-the-opioid-epidemic-dr-anna-lembke-discusses-48277528>
11. Nov 2016 *Straight Talk MD with Frank Sweeny* invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
<http://straighttalkmd.com/podcast/drug-dealer-md-opioid-epidemic-anna-lembke-md/>
12. Nov 2016 *Conversation on Healthcare Reach MD Radio*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
<http://www.chcradio.com/episode.php?id=360>
13. Nov 2016 *KALW Local Public Radio*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
<http://kalw.org/post/city-visions-how-doctors-fueled-opioid-epidemic#stream/0>
14. Nov 2016 *Forum with Michael Krasny (KQED-FM)* invited panelist to discuss “The Surgeon General’s Report: Facing Addiction in America,”
<https://ww2.kqed.org/forum/2016/11/28/addiction-is-illness-not-a-moral-failing-says-surgeon-general/>
15. Nov 2016 *Stanford Scope 1:2:1 Podcast with Paul Costello* invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*

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<http://med.stanford.edu/news/all-news/one-to-one/2016/drug-dealer--md--how-physicians-are-fueling-the-opioid-epidemic.html>

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night-with-megyn-kelly/3536915

26. June 2017 *KCBS Radio in San Francisco* invited guest to discuss the ongoing opioid epidemic
27. July 2017 KPCC's AirTalk with host Larry Mantle, live guest appearance to discuss the opioid crisis <http://www.scpr.org/programs/airtalk/2017/07/20/58084/in-the-context-of-the-opioid-crisis-doctors-discus/>
28. July 2017 Jose Calderon Mindful Psychiatry Live Radio and Podcast, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <http://wholebodymentalhealth.libsyn.com/hard-pill-to-swallow-drug-dealer-md-with-dr-anna-lempke-md-7-5-17>
29. Aug 2017 KQED Forum with Michael Krasny Live Radio Broadcast, invited guest to discuss *Rise in High-Risk Drinking a Public Health Crisis, New Study Finds*
30. Aug 2017 MSNBC with Chris Hayes, live guest appearance to discuss President Trumps inaction on the opioid epidemic <http://www.msnbc.com/all-in/watch/donald-trump-has-done-nothing-on-the-opioid-crisis-1032009795986>
31. Sept 2017 KPCC's AirTalk with host Larry Mantle, live guest appearance to discuss CVS Pharmacy's announcement it will limit opioid prescriptions to seven days for certain conditions for new patients seeking drugs for pain relief.
<http://www.scpr.org/programs/airtalk/2017/09/22/59288/how-much-would-cvs-s-7-day-limit-on-painkiller-pre/>
32. Oct 2017 BBC Newshour on BBC World Service radio on the opioid epidemic with host James Menendez <http://www.bbc.co.uk/programmes/w172vghc8jkrr3g>
33. Oct 2017 NBCUniversal live in the studio with Dr. John Torres, One Nation Overdosed: Doctors Speak Out <http://qlnk.io/ql/59f0f15be4b0945e5d8ff73f>
34. Oct 2017 KPIX 5 CBS San Francisco Trump declares the opioid epidemic a public health emergency <http://sanfrancisco.cbslocal.com/video/3752604-critics-say-trumps-opioid-announcement-doesnt-go-far-enough/>
35. Oct 2017 KPIX 5 CBS San Francisco commentator on bay area parents using marijuana <http://sanfrancisco.cbslocal.com/2017/11/04/marin-mom-marijuana-makes-her-better-parent/>
36. Jan 2018 KQED with Brian Watt on “smartphone addiction”
<https://soundcloud.com/kqed/investors-urge-apple-to-take-action-to-curb-digital-device-overuse-among-children>

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37. Feb 2018 Sirius/XM radio with Clare Marie Gauthier, Co-Host, Dave Nemo Weekends, RadioNemo of North America, on the opioid epidemic and *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
38. Feb 2018 KQED News radio, report on Purdue Pharma's decision to stop marketing opioids directly to doctors
39. Feb 2018 NPR Smartphone Detox, How to Power Down in a Wired World
<https://www.npr.org/sections/health-shots/2018/02/12/584389201/smartphone-detox-how-to-power-down-in-a-wired-world>
40. Mar 2018 Sirius/XM Radio with Clare Marie Gauthier, Co-Host, Dave Nemo Weekends, RadioNemo of North America, on addiction treatment
41. Mar 2018 Sirius/XM Radio "Doctor Radio", on the silent benzodiazepine epidemic
42. Mar 2018 Sirius XM Radio: POTUS Channel 124, "Steele & Ungar", on new Center for Medicare and Medicaid Services regulations to restrict opioid prescribing
43. Mar 2018 KPCC's AirTalk with host Larry Mantle, live guest appearance to discuss new Center for Medicare and Medicaid Services regulations to restrict opioid prescribing
44. Mar 2018 Science VS. with Rose Rimler, "Opioids: Kicking America's Addiction"
<https://www.gimletmedia.com/science-vs/opioids-kicking-americas-addiction#episode-player>
45. April 2018 KQED Forum with Michael Krasny, Medical Community Divided On Medicare's Policy to Shorten High-Dose Opioid Prescriptions,
<https://www.kqed.org/forum/2010101864587/medical-community-divided-on-medicares-policy-to-shorten-high-dose-opioid-prescriptions>
46. May 2018 Radio Health Journal with Reed Pence: The Opioid Epidemic,
http://mediatracks.com/shows/RHJ_18-17.mp3
47. May 2018 Straight Talk MD: Health | Medicine | Healthcare Policy | Health Education | Anesthesiology, The Cannabis Conversations: Part II with Anna Lembke MD
<http://straighttalkmd.com/podcast/the-cannabis-conversations-part-ii-with-anna-lembke-md/>
48. June 2018 The Future of Everything with Russ Altman (Stanford Radio), 06/18/18. In a recent segment on Stanford Radio, Russ Altman discussed the rise of the opioid epidemic in the United States with Anna Lembke. <https://soundcloud.com/user-458541487/facing-addiction-with-guest-anna-lembke>

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49. July 2018 NBC News with Dr. John Torres to discuss benzodiazepines https://www.nbcnews.com/nightly-news/video/is-anti-anxiety-medication-the-next-u-s-drug-crisis-1287215683720?cid=eml_onsite
50. Oct 2018 NOVA/PBS documentary ADDICTION, Produced, Directed and Written by Sarah Holt, Co-producer Julie Crawford <http://www.holtproductions.org>; <http://www.pbs.org/wgbh/nova/body/addiction.html>
51. Mar 11, 2019 Spectrum News In Focus, What's Causing the Opioid Crisis, with Renee Eng, <https://spectruminfocus.com/section/in-focus/in-focus/2019/03/11/in-focus--what-s-causing-the-opioid-crisis#>
52. April 29, 2019 KALW City Visions, California's drug rehabilitation industry, <https://www.kalw.org/post/city-visions-reforming-californias-drug-rehabilitation-industry#stream/0>
53. May 20, 2019 Groundless Ground podcast with Lisa Dale Miller, Chronic Pain, Dual-Diagnosis and Addiction Treatment, <https://groundlessground.com/episodes/anna-lembke-chronic-pain-dual-diagnosis-and-addiction-treatment>
54. June 24, 2019 KCBS News Radio San Francisco 10 Q's w/Stan & Susan, to discuss rising rates of fentanyl overdose in San Francisco <https://kcbsradio.radio.com/blogs/margie-shafer/fentanyl-becomes-san-francis>
55. July 18, 2019 Russian Television News (RT International) "The Opioid Epidemic in the United States: Where Are We Now?" <https://www.youtube.com/watch?v=KP-Vn2d6LWk>
56. Aug 26, 2019 Russian Television News (RT International) on the Oklahoma vs Johnson & Johnson opioid litigation <https://youtu.be/sNKRMYIrPtE>
57. Aug 29, 2019 Monocle 24 Radio in London on the opioid crisis in follow up to the outcome of the Oklahoma vs Johnson & Johnson opioid litigation
58. Sept 2019 American Journal of Psychiatry Residents' Journal podcast series <http://ajpresidentsjournal.apapublishing.libsynpro.com>
59. Sept 2019 The Voice of Medicine podcast, m.hulik@radiolutions.com
60. Oct 2019 This is Life with Lisa Ling, Benzodiazepines, <https://www.cnn.com/2019/10/04/health/benzodiazepines-this-is-life-with-lisa-ling/index.html> ; <https://itunes.apple.com/us/tv-season/this-is-life-with-lisa-ling-season-6/id1480545936>

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61. Oct 2019 Straight Talk with Frank Sweeny, Benzodiazepines,
<https://podcasts.apple.com/us/podcast/straight-talk-md-health-medicine-healthcare-policy/id1060256849#episodeGuid=78d97afe7ea14dac8261193a2aa3d69> ;
<https://open.spotify.com/episode/1jrtfq60dmraRnzTtsUNeb?si=jO2RZqjDTM-c1VJUVsWcuw>
62. Dec 2019 CBSN Bay Area, 12/09/19 Medical Monday: How to avoid overindulging in alcohol during the holiday season and setting healthy drinking limits
<https://sanfrancisco.cbslocal.com/live/cbsn-bay-area/video/3439448-20191209162159-medical-mondays-dr-anna-lembke-addiction-recovery-relapse-triggers/>
63. Feb 2020 Netflix's "The Pharmacist" explores how pill mill doctors fanned the flames of the country's opioid epidemic by flagrantly overprescribing three particular drugs. Anna Lembke, associate professor of psychiatry and behavioral sciences, is quoted in this piece. <https://www.oxygen.com/true-crime-buzz/oxycontin-soma-xanax-the-holy-trinity-from-the-pharmacist-explained>
64. Feb 2020 What Makes Up Your Mind: Opioids And Addiction with Dr. Anna Lembke, Stanford University Department of Psychiatry Podcast,
<https://m.soundcloud.com/stanfordpsy/february2020/s-kBmxv>
65. Feb 2020 Sirius XM Doctor Radio, invited guest to discuss benzodiazepines, Scott.Uhing@SiriusXM.com
66. Mar. 2020, "The Defining Moments of the Opioid Epidemic,
<https://www.mdmag.com/medical-news/defining-moments-opioid-epidemic>
67. Mar. 2020, Redefining Medicine with special guest Dr Anna Lembke,
<https://www.youtube.com/watch?v=6AYSavowleA>
68. April 2020 Doc to Doc with Dr. John Torres, Medical Correspondent NBC News and MSNBC, Facebook Live, *Mental Health During Quarantine*
69. July 2020 The Therapy Show with Dr. Bridget Nash,
<https://www.therapyshow.com/podcasts/episode/2986f561/drug-dealer-md-author-dr-anna-lembke-discusses-the-latest-treatments>

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Anna Lembke, M.D. Report

EXHIBIT B

List of Materials Considered

Materials Considered

1. Abigail Zuger, *A Doctor's Guide to What to Read on the Opioid Crisis*, N.Y.Times (Dec. 17, 2018)
2. Achenbach, Joel. New Guidelines on Opioid Tapering Tells Doctors to Go Slow. Washington Post (Oct. 10, 2019)
3. Adams EH, et al. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. *J Pain Symptom Manage* 2006; 31:465–76.
4. Adams EH. A study of Avinza ® (morphine sulfate extended-release capsules) for chronic moderate-to-severe noncancer pain conducted under real-world treatment conditions—The ACCPT Study. *Pain Practice* 2006; 6(4):254-264.
5. Adewumi, Adeleke D. et al. Prescription Opioid Fatalities: Examining Why the Healer Could be the Culprit, *Drug Saf*, 2018
6. Afilalo, M., Efficacy and Safety of Tapentadol Extended Release Compared with Oxycodone Controlled Release for the Management of Moderate to Severe Chronic Pain Related to Osteoarthritis of the Knee A Randomized, Double-Blind, Placebo- and Active-Controlled Phase III Study, *Clinical Drug Investigation* 30:489 (2010)
7. Agency for Healthcare Research and Quality, Medication-Assisted Treatment Models of Care for Opioid Use Disorder in Primary Care Settings (2016)
8. Agrawal S, et al. The Sunshine Act—effects on physicians. *N Engl J Med*. 2013;368(22):2054–2057.
9. Ahmad FB, et al. Provision Drug Overdose Death Counts. National Center for Health Statistics. NVSS. Vital Statistics Rapid Release
10. Ahmed SH, Imbalance between drug and non-drug reward availability: a major risk factor for addiction. *Eur J Pharmacol*. 2005; 526(1–3):9-20.
11. Aitken P, et al. A Single Dose, Four-Way, Open-Label Bioavailability Study of Oral Acetaminophen and Ibuprofen Combinations (Maxigesic) Under both Fasting and Fed Conditions. *J. Bioequiv Availab* (2018)
12. Ajay Manhapra MD, Albert J. Arias MD & Jane C. Ballantyne MD (2018) The conundrum of opioid tapering in long-term opioid therapy for chronic pain: A commentary, *Substance Abuse*, 39:2, 152-161

*Lembke Report**Confidential — Subject to Protective Order*

13. Ali MM, Cutler E, Mutter R, Henke RM, O'Brien PL, Pines JM, Mazer-Amirshahi M, Diou-Cass J. Opioid Use Disorder and Prescribed Opioid Regimens: Evidence from Commercial and Medicaid Claims, 2005-2015. *J Med Toxicol.* 2019
14. Allan L, et al. Randomized crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *BMJ* 2001; 322.
15. Allan, L. Transdermal fentanyl versus sustained release oral morphine in strong- opioid naïve patients with chronic low back pain. *Spine* 2005; 30(22):2484-2490
16. American Academy of Family Physicians. Clinical Practice Guidelines Opioid Prescribing for Chronic Pain (April 2016)
17. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders. Washington, DC. American Psychiatric Association; 2013.
<https://doi.org/10.1176/appi.books.9780890425596>
18. American Society of Addiction Medicine Definition of Addiction. Public Policy Statement: Definition of Addiction, ASAM. <https://www.asam.org/resources/definition-of-addiction>. Accessed June 20, 2018.
19. Anderson TS et al. Financial payments to teaching hospitals by companies marketing opioids. *J. General Internal Medicine* (2019), at p. 1.
20. Anderson VC, Ph D, et al. Prospective Study of Long-term Intrathecal Morphine in the Management of Chronic Nonmalignant Pain. 1999;44(2)
21. Anora M. Gaudiano, How the opioid epidemic is exacerbating a US labor-market shortage. MarketWatch, June 29, 2018. <https://www.marketwatch.com/story/how-the-opioid-epidemic-is-exacerbating-a-us-labor-market-shortage-2018-06-28>
22. Anora M. Gaudiano, How the opioid epidemic is exacerbating a US labor-market shortage. MarketWatch, June 29, 2018. <https://www.marketwatch.com/story/how-the-opioid-epidemic-is-exacerbating-a-us-labor-market-shortage-2018-06-28>.
23. Anthony, James C., Lynn A. Warner, and Ronald C. Kessler. "Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey." (1997).
24. Arkinstall W, Efficacy of controlled-release codeine in chronic non-malignant pain: a randomized, placebo-controlled clinical trial. *Pain* 1995; 62: 169-178.
25. Aronoff G. Opioids in chronic pain management: is there a significant risk of addiction, *Current Rev Pain* 2000;4:112-121.

*Lembke Report**Confidential — Subject to Protective Order*

26. Ashburn, M. et al. Increasing Evidence for the Limited Role of Opioids to Treat Chronic Noncancer Pain. *JAMA*. 2018;320(23):2427-2428. doi:10.1001/jama.2018.19327
27. ASPPH 2019 Report and Recommendations from the ASPPH Task Force On Public Health Initiatives to Address the Opioid Crisis
28. ASPPH Task Force on Public Health Initiatives to Address the Opioid Crisis. Bringing Opioids to Bear on Opioids: Report and Recommendation from the ASPPH Task Force on Public Health Initiatives to Address the Opioid Crisis. November 2019
29. Atluri S, et al. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain Physician*. 2014.
30. Ayoobi F, et al. Impact of Opium Dependency on Clinical and Neuropsychological Indices of Multiple Sclerosis Patients, *Neurological Sciences* (2019)
31. Azad, Lembke, A. et al, Patterns of Opioid and Benzodiazepine Use in Opioid-Naïve Patients with Newly Diagnosed Low Back and Lower Extremity Pain, , *J Gen Intern Med*, 2019, 35(1):291-297. doi: 10.1007/s11606-019-05549-8.
32. Baker D. History of the Joint Commission's Pain Standards Lessons for Today's Prescription Opioid Epidemic. *JAMA* (2017)
33. Baker DW, History of The Joint Commission's Pain Standards: Lessons for Today's Prescription Opioid Epidemic. *JAMA*. 2017 Mar 21;317(11):1117-1118. doi: 10.1001/jama.2017.0935. No abstract available. PMID:28241189
34. Baker DW. The Joint Commission and the Opioid Epidemic-Reply. *JAMA*. 2017 Jul 4; 318(1):92. doi: 10.1001/jama.2017.6701. No abstract available. PMID: 28672313
35. Ballantyne, et al. Opioid Therapy for Chronic Pain, *N Engl J Med*, 2003; 349; 1943-53
36. Banta-Green CJ, et al. Opioid use behaviors, mental health and pain— development of a typology of chronic pain patients. *Drug Alcohol Depend* 2009; 104:34–42.
37. Barocas, J. et al. Estimated Prevalence of Opioid Use Disorder in Massachusetts, 2011–2015: A Capture–Recapture Analysis. *Am J Public Health*. 2018;108:1675– 1681. doi:10.2105/AJPH.2018.304673
38. Baron MJ, McDonald PW. Significant pain reduction in chronic pain patients after detoxification from high-dose opioids. *J Opioid Manage* 2006;2 (5):277–82.
39. Bartleson JD, Evidence for and against the use of opioid analgesics for chronic nonmalignant low back pain: a review, *Pain Med* 2002;3(3):260-271.

*Lembke Report**Confidential — Subject to Protective Order*

40. Bateman, Brian T., et al. Patterns of opioid prescription and use after cesarean delivery. *Obstetrics and gynecology* 130.1 (2017): 29.
41. Beauchamp G, et al. Moving beyond misuse and diversion: the urgent need to consider the role of iatrogenic addiction in the current opioid epidemic. *Am J Public Health*. 2014; 104(11):2023–2029.
42. Becker WC, et al. Non-medical use, abuse and dependence on prescription opioids among U.S. adults: psychiatric, medical and substance use correlates. *Drug Alcohol Depend* 2008;94:38-47
43. Bedson J, Chen Y, Ashworth J, Hayward RA, Dunn KM, Jordan KP. Risk of adverse events in patients prescribed long-term opioids: A cohort study in the UK Clinical Practice Research Datalink. *Eur J Pain*. 2019
44. Belgrade MJ, Non-compliant drug screens during opioid maintenance analgesia for chronic non-malignant pain. Am. Pain Society Meeting 2001; San Diego A# 787, p 42
45. Belkin M, Reinheimer HS, Levy J, Johnson B. Ameliorative response to detoxification psychotherapy, and medical management in patients maintained on opioids for pain. *Am J Addict* 2017;26 (7):738–43.
46. Ben Gitis, Isabel Soto, The Labor Force and Output Consequences of the Opioid Crisis, American Action Forum (Mar. 27, 2018),
<https://www.americanactionforum.org/research/labor-force-output-consequences-opioid-crisis/>.
47. Berna C, et al. Tapering Long-Term Opioid Therapy in Chronic Noncancer Pain: Evidence and Recommendations for Everyday Practice. *May Clin Proc*. June 2015;90(6):828-842
48. Beyer CA, Poltavskiy E, Walker LE et. al., Persistent Opioid Use After Combat Injury and Subsequent Long-term Risk of Abuse: a retrospective cohort study *Annals of Surgery*, 2019
49. Bicket, Mark C., et al. Association of new opioid continuation with surgical specialty and type in the United States. *The American Journal of Surgery* (2019).
50. Binsfeld, Heinrich, et al. "A Randomized Study to Demonstrate Noninferiority of Once-Daily OROS® Hydromorphone with Twice-Daily Sustained-Release Oxycodone for Moderate to Severe Chronic Noncancer Pain." *Pain Practice* 10.5 (2010): 404-415.

51. Blondell RD, et al. A Clinical Trial Comparing Tapering Doses of Buprenorphine with Steady Doses for Chronic Pain and Co-Existent Opioid Addiction. *J Addict Med.* 2010 September ; 4(3): 140–146
52. Bloodworth D. Issues in opioid management, *Am J Phys Med Rehabil* 2005; 84:S42-S55.
53. Bloom, Josh. The Opioid Epidemic In 6 Charts Designed To Deceive You, American Council on Science and Health, 2018
54. Bluethmann SM, et al. Anticipating the silver tsunami: Prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev.* 2016. doi:10.1158/1055-9965.EPI-16-0133.
55. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the “silver tsunami”: Prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev.* 2016. doi:10.1158/1055-9965.EPI-16-0133, at p. 1029.
56. Bohnert AS, et al. Prescribing in the United States Before and After the Centers for Disease Control and Prevention’s 2016 Opioid Guideline. *Ann Intern Med.* 2018.
57. Bohnert ASB, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA - J Am Med Assoc.* 2011;305(13):1315-1321
58. Bohnert ASB, et al. Understanding Links among Opioid Use, Overdose, and Suicide. *N Engl J Med.* 2019. doi:10.1056/nejmra1802148
59. Bohnert, ASB, et al. A Detailed Exploration Into the Association of Prescribed Opioid Dosage and Overdose Deaths Among Patients With Chronic Pain. *Medical Care* 2016; 54:435-441
60. Bolshakova M, Bluthenthal R, Sussman S, Opioid Use and Misuse: health impact, prevalence, correlates and interventions. *Psychology & Health* (2019)
61. Bonnie, R. et al. Pain Management and the Opioid Epidemic Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. NASEM. 2017. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24781>
62. Borghouts JA, The clinical course and prognostic factors of non-specific neck pain: a systematic review, *Pain* 1998; 77:1-13.
63. Boscarino J A, et al. Factors associated with opioid overdose: a 10-year retrospective study of patients in a large integrated health case system. *Substance Abuse and Rehabilitation* 2016:7 131–141

64. Boscarino J A, et al. Opioid-use disorder among patients on long-term opioid therapy: impact of final DSM-5 diagnostic criteria on prevalence and correlates. Dove Press. Substance Abuse and Rehabilitation 2015;6 83-91
65. Boscarino J, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. J Addict Dis. 2011;30(3):185-194. doi:10.1080/10550887.2011.581961
66. Bouckoms AJ, et al. Chronic nonmalignant pain treated with long-term oral narcotic analgesics. Ann Clin Psychiatry 1992; 8:185–92
67. Boyd CJ, et al. Medical and nonmedical use of prescription pain medication by youth in a Detroit-area public school district. Drug Alcohol Depend. 2006. doi:10.1016/j.drugalcdep.2005.05.017
68. Branch v Purdue Pharma et al. No. LR 1696-3, 2004 WL 3752789 (Tex. Dist. Richmond Civil)
69. Broughton AN, Long term tolerability of cr oxycodone (OxyContin tablets) in 101 patients treated for 12 months, World Congress On Pain 1999; 339.
70. Brown J, et al. Assessment, stratification, and monitoring of the risk for prescription opioid misuse and abuse in the primary care setting. J Opioid Manag 2011; 7:467–83.
71. Bruce Gundy Linkedin Profile, <https://www.linkedin.com/in/bruce-gundy-5b5085a>
72. Bruguera P, Heavy Prescription Over Time Leading to Opioid Dependence. Journal of Substance Use (2018)
73. Brummett CM, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. JAMA Surg. 2017 Jun 21; 152(6): e170504
74. Bucher C, The Role of Transdermal Compounding in Opioid Safety. Journal of Opioid Management (2018)
75. Burchman SL, Implementation of a formal treatment agreement for outpatient management of chronic nonmalignant pain with opioid analgesics, Journal of Pain and Symptom Management 1995; 10 (7).
76. Burke LG, et al. Trends in opioid use disorder and overdose among opioid-naïve individuals receiving an opioid prescription in Massachusetts from 2011 to 2014. *Addiction*. 2019;1-12, at p. 9

*Lembke Report**Confidential — Subject to Protective Order*

77. Burton, A, et al. Illicit Substance abuse via an implanted intrathecal pump, Anesthesiology Nov. 1998, Vol.89, 1264-1267. doi:
78. Busse, Jason, et al. In Reply. Meta-analysis of Opioids for Chronic Pain. JAMA May 21, 2019 Volume 321, Number 19. 1934-36Opioids for Chronic Noncancer Pain. A Systematic Review and Meta-analysis. JAMA. 2018;320(23):2448-2460
79. Busse, Jason, et al. Opioids for Chronic Noncancer Pain. A Systematic Review and Meta-analysis. JAMA. 2018;320(23):2448-2460
80. Butler SF, et al. Cross validation of the Current Opioid Misuse Measure (COMM) to monitor chronic pain patients on opioid therapy. Clin J Pain 2010; 26:770–6.
81. Butler SF, et al. Validation of a screener and opioid assessment measure for patients with chronic pain. Pain 2004; 112:65–75.
82. Butler, Stephen , Tapentadol Abuse Potential: A Postmarketing Evaluation Using a Sample of Individuals Evaluated for Substance Abuse Treatment, Pain Medicine (2015) 16:119-130
83. Buynak, R., Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study, Expert Opin. Pharmacother. (2010) 11(11):1787-1804.
84. Buynak, Robert, et al. Long-term safety and efficacy of tapentadol extended release following up to 2 years of treatment in patients with moderate to severe, chronic pain: results of an open-label extension trial. Clinical therapeutics 37.11 (2015): 2420-2438.
85. Cabell ER visits for drug overdose ER visits for 2019-2020
86. Cadoni C, et al. Behavioral sensitization after repeated exposure to Delta 9-tetrahydrocannabinol and cross-sensitization with morphine. Psychopharmacol. 2001; 158(3):259–266.
87. Caldwell JR, Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: Results from a randomized, placebo- controlled, double-blind trial and an open-label extension trial. Journal of Pain and Symptom Management 2002; 23 (4). 278-291
88. Caldwell JR, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal anti-inflammatory drugs: A double blind, randomized, multicenter, placebo controlled trial. The J. of Rheumatology 1999, 26(4), 862-69

*Lembke Report**Confidential — Subject to Protective Order*

89. California Opioid Overdose Surveillance Dashboard <https://skylab.cdph.ca.gov/ODdash/>
90. Campbell UC, et al. Acquisition of drug self-administration: environmental and pharmacological interventions. *Exp Clin Psychopharmacol.* 2000;8:312–325.
91. Campbell v Purdue Pharma et al, No. 1:02CV00163TCM, 2004 WL 6057307 (E.D. Missouri 2004)
92. Candiotti, Keith M.D., Use of Opioid Analgesics in Pain Management, Prescribe Responsibly, <http://www.prescriberesponsibly.com/articles/opioid-pain-management>.
93. Carlson C, et al. State Boards of Nursing Guidance to Mitigation Prescription Opioid Misuse and Diversion. *Pain Management Nursing* (2019)
94. Case A. et al. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci.* 2015. doi:10.1073/pnas.1518393112
95. Catan T, et al. A Pain Drug Champion Has Second Thoughts. *The Wall Street Journal.* December 2012.
96. CDC Data & Statistics on Sickle Cell Disease
<https://www.cdc.gov/ncbddd/sicklecell/data.html>
97. CDC Drug Overdose Death Data
<https://www.cdc.gov/drugoverdose/data/statedeaths.html>
98. CDC. Opioids for Acute Pain: Get the Facts
<https://www.cdc.gov/drugoverdose/pdf/patients/Get-the-Facts-a.pdf>
99. CDC. Pocket Guide: Tapering Opioids for Chronic Pain.
100. Celebrex label (2005), *see*
https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020998s017lbl.pdf at pp. 4, 6-7
101. Center for Behavioral Health Statistics and Quality, 2016 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD.
102. Centers for Disease Control and Prevention, Data Brief 329. Drug Overdose Deaths in the United States, 1999–2017. https://www.cdc.gov/nchs/data/databriefs/db329_tables-508.pdf#page=1, at p. 4.

*Lembke Report**Confidential — Subject to Protective Order*

103. Centers for Disease Control and Prevention, *Data Brief 356. Drug Overdose Deaths in the United States, 1999–2018*, at Data Table for Figure 3, https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf.
104. Centers for Disease Control and Prevention. *Prescription Opioids*. <https://www.cdc.gov/drugoverdose/opioids/prescribed.html> (last updated August 29, 2017)
105. Centers for Disease Control and Prevention. *Prescription Painkiller Overdoses in the US infographic*. <https://www.cdc.gov/vitalsigns/painkilleroverdoses/infographic.html>, (last updated November 1, 2011).
106. Centers for Disease Control and Prevention. U.S. County Prescribing Rate Maps (2012), <https://www.cdc.gov/drugoverdose/maps/rxcounty2012.html>
107. Centers for Disease Control and Prevention. U.S. County Prescribing Rate Maps (2017), <https://www.cdc.gov/drugoverdose/maps/rxcounty2017.html>
108. Centers for Disease Control and Prevention. U.S. Prescribing Rate Maps (2006- 2018), Centers for Disease Control and Prevention.
<https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html>.
109. Centers for Disease Control and Prevention. What States Need to Know about PDMPs. <https://www.cdc.gov/drugoverdose/pdmp/states.html>
110. Centers for Disease Control, Opioid Basics: Fentanyl
<https://www.cdc.gov/drugoverdose/opioids/fentanyl.html>
111. Cepeda, MS *et al.* Comparison of the risks of opioid abuse or dependence between tapentadol and oxycodone: results from a cohort study. *Journal of Pain*. 2013;14(10): 1227-1241 at p. 1227.
112. Cepeda,SM., Comparison of Opioid Doctor Shopping for Tapentadol and Oxycodone: A Cohort Study, *Journal of Pain* 14:1227 (2013)
113. Chabal C, Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors, *Clin J Pain* 1997;13(2):150-155
114. Chang AK, et al. Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. *JAMA*. 2017;318(17):1661–1667. doi:10.1001/jama.2017.16190, at p.1661.
115. Chao J, Retrospective analysis of Kadian (morphine sulfate sustained-release capsules) in patients with chronic, nonmalignant pain, *Pain Medicine* 2005; 6 (3): 262-5.

*Lembke Report**Confidential — Subject to Protective Order*

116. Chaparro LE, et al. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database Syst Rev. 2013. doi:10.1002/14651858.CD004959.pub4
117. Chaparro LE, et al. Opioids compared with placebo or other treatments for chronic low back pain: An update of the Cochrane review. SPINE Volume 39, Number 7 , pp 556 - 563. Spine (Phila Pa 1976). 2014. doi:10.1097/BRS.0000000000000249
118. Chapman C, Prolonged morphine self-administration and addiction liability. Evaluation of two theories in a bone marrow transplant unit, Cancer 1989;63:1636-1644
119. Cheatle MD, Balancing the Risks and Benefits of Opioid Therapy for Patients with Chronic Nonmalignant Pain: have we gone too far or not far enough?. Pain Medicine (2018)
120. Cheatle MD, Gallagher RM. Chronic Pain and Opioids. Handbook of Pain and Palliative Care.
121. Cheatle MD, Prescription Opioid Misuse, Abuse, Morbidity, and Mortality: Balancing Effective Pain Management and Safety. Pain Med. 2015 Oct; 16 Suppl 1:S3-8. doi: 10.1111/pme.12904. Epub 2015 Sep 11.
122. Chelminski PR, et al. A primary care, multi- disciplinary disease management program for opioid-treated patients with chronic non-cancer pain and a high burden of psychiatric comorbidity. BMC Health Serv Res 2005;5:3.
123. Chen JH, et al. Distribution of opioids by different types of Medicare prescribers. JAMA Intern Med. December 2015:1–3.
124. Chen LH, et al. Rates of deaths from drug poisoning and drug poisoning involving opioid analgesics—United States, 1999–2013. MMWR Morb Mortal Wkly Rep. 2015; 64(32). <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6401a10.htm>
125. Chen T-C, et al. A 15-year overview of increasing tramadol utilization and associated mortality and the impact of tramadol classification in the United Kingdom. *Pharmacoepidemiol Drug Saf.* 2018;27:487-494, at p. 487.
126. Chhabra N, et al. The Joint Commission and the Opioid Epidemic, JAMA. 2017 Jul 4; 318(1):91-92. doi: 10.1001/jama.2017.6694. No abstract available.PMID:28672310
127. Child Trends Foster Care WV Federal Fiscal Year 2015
128. Chin KY, Mark-Lee WF, A Review on the Antinociceptive Effects of Mitragyna Speciosa and Its Derivatives on Animal Model. Current Drug Targets (2018).

*Lembke Report**Confidential — Subject to Protective Order*

129. Chisholm-Burns MA, Spivey CA, Wheeler J, Hohmeier K, The Opioid Crisis: Origins, Trends, Policies and the Roles of Pharmacists. *American Journal of Health-System Pharmacy* (2019)
130. Chou R, Deyo R, Devine B, *et al.* The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. *Evid Rep Technol Assess (Full Rep)*. 2014;218(218):63. doi:10.23970/AHRQEPERTA218 at p. ES-1
131. Chou R, Turner J a., Devine EB, *et al.* The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015;162(4). doi:10.7326/M14-2559, at p. 276 (emphasis added.)
132. Chou R. Clinical Guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Journal of Pain*. 2009;10(2):113-130 at p. 130.e5.
133. Chou, et al., Rethinking Opioid Dose Tapering, Prescription Opioid Dependence, and Indications for Buprenorphine, *Ann Intern Med*. 2019;171(6):427-429.
134. Chou, R, et al. Nonpharmacologic therapies for low back pain: A systematic review for an American College of physicians clinical practice guideline. *Ann Intern Med*. 2017. doi:10.7326/M16-2459
135. Chou, R, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. , *Ann Intern Med*. 2017; 166:480-492. doi:10.7326/M16-2458
136. Chou, R, et al. The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. *Ann of Intern Med*. 2015;162:276-286. doi:10.7326/M14-2559
137. Chou, R, et al. The effectiveness and risks of long-term opioid treatment of chronic pain, Agency for Healthcare Research and Quality Publication. *Evid Rep Technol Assess*. 2014; (218). <http://www.ncbi.nlm.nih.gov/books/NBK258809/>.
138. Chou, R. et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain , *J. Pain* 2009; 10:113-130
139. Chris Nicholson "Teva to Buy Cephalon for \$6.8 Billion" New York Times (May 2nd, 2011)
140. Chris Zimmerman Linkedin Profile, <https://www.linkedin.com/in/chriszimmerman>

141. Cicero TJ, et al. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA Psychiatry*. 2014.
142. Cicero, Theodore J. et al. Increased use of Heroin as an Initiating Opioid of Abuse, *Addictive Behaviors*, 2017; 74; 63–66
143. City of Burlington, Mayor's Office, Press Release, Mayor Miro Weinberger and Community Partners Announce 50 Percent Decline in Opioid-Related Overdose Fatalities in Chittenden County in 2018 (February 14, 2019). See <https://www.burlingtonvt.gov/Press/mayor-miro-weinberger-and-community-partners-announce-50-percent-decline-in-opioid-related>.
144. Clark MR, et al. Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population. *Pain Med*. 2018; 19(7):1382- 1395. <http://dx.doi.org/10.1093/pmt/pnx332>
145. Coalition on Chronic Pain Management 2019 Report to the Legislature, West Virginia Legislature.
146. Coloma-Carmona A, et al. Medical and Psychological Predictors of Prescription Opioids Dependence During Chronic Pain Treatment. *Revue européenne de psychologie appliquée* (2018)
147. Coloma-Carmona A, et al. Withdrawal Symptoms Predict Prescription Opioid Dependence in Chronic Pain Patients. *Drug and Alcohol Dependence* (2019)
148. Compton PA, et al. Introduction of a self-report version of the Prescription Drug Use Questionnaire and relationship to medication agreement non-compliance. *J Pain Symptom Manage* 2008; 36:383–95.
149. Compton WM, et al. Relationship between nonmedical prescription-opioid use and heroin use. *N Engl J Med*. 2016; 374:154–163.
150. Compton WM, Jones SM, Epidemiology of the US Opioid Crisis: the importance of the vector. *Ann. N.Y. Acad. Sci.* (2019)
151. Cook DJ, Kaskovich SW, Pirkle SC, Mica MAC, Shi LL, Lee MJ. Benchmarks of Duration and Magnitude of Opioid Consumption After Total Hip and Knee Arthroplasty: A Database Analysis of 69,368 Patients. *J Arthroplasty*. 2019
152. Cornett EM, Budish R, Latimer D, Hart B, Urman RD, Kaye AD, Management of Challenging Pharmacologic Issues in Chronic Pain and Substance Abuse Disorders. *Anesthesiology Clin* (2019)

153. Cosgrove, Lisa, and Sheldon Krimsky. "A comparison of DSM-IV and DSM-5 panel members' financial associations with industry: a pernicious problem persists." *PLoS Med* 9.3 (2012): e1001190.
154. Courtney Hessler "65 million opioids flooded Cabell County over 7 years" *Herald Dispatch* July 19, 2019
155. Courtwright DT. Dark Paradise: A History of Opiate Addiction in America. Harvard University Press; 2001
156. Couto JE, et al. High rates of inappropriate drug use in the chronic pain population. *Popul Health Manag* 2009; 12:185–90.
157. Cowan D. Problematic terminology for problematic drug use. *J Opioid Manage* 2006;2 (1) 23-30.
158. Cowan DT, et al. A pilot study into the problematic use of opioid analgesics in chronic non-cancer pain patients. *Int J Nurs Stud* 2002; 39:59–69
159. Cowan DT, et al. A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. *Pain Med* 2005; 6:113–21
160. Cowan DT, et al. A survey of chronic noncancer pain patients prescribed opioid analgesics. *Pain Med* 2003; 4:340–51
161. Crews F, et al. Adolescent cortical development: a critical period of vulnerability for addiction. *Pharmacol Biochem Behav*. 2007;86(2):189-199.
doi:10.1016/j.pbb.2006.12.001
162. Ctrs. for Disease Control and Prevention, *Opioid Overdose*,
<https://www.cdc.gov/drugoverdose/index.html>: “Drug overdose deaths continue to increase in the United States.
163. Ctrs. for Disease Control and Prevention, What States Need to Know about PDMPs.
<https://www.cdc.gov/drugoverdose/pdmp/states.html>.
164. Ctrs. for Disease Control and Prevention. *U.S. Opioid Prescribing Rate Maps*.
<https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html>. See Appendix III to this Report, providing comparative, and substantially higher prescribing rates for West Virginia and Cabell County. In some years, the Cabell County prescribing rates were more than double the national average.

165. Cts. for Disease Control and Prevention. *Synthetic Opioid Overdose Data*, (Apr. 2, 2019) <https://www.cdc.gov/drugoverdose/data/fentanyl.html>.
166. Cunningham JL, et al. Opioid tapering in fibromyalgia patients: Experience from an interdisciplinary pain rehabilitation program. *Pain Med (United States)*. 2016. doi:10.1093/pmv/nv079
167. Cuyahoga County Community Health Assessment 2018/2018 Community Health Needs Assessment Adeopted by University Hostpitals on September 27, 2018
168. Cuyahoga County Medical Examiner's Office. Heroin/Fentanyl/Cocaine Related Deaths in Cuyahoga County. August 8,2019. http://medicalexaminer.cuyahogacounty.us/pdf_medicalexaminer/en-US/HeroinFentanylReports/080819-HeroinFentanylReport.pdf
169. da Costa BR, Nuesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip (Cochrane Review). 2014, at p. 28.
170. da Costa, Bruno, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip, Cochrane Database of Systematic Reviews 2014; (9):CD003115
171. Daniels, Stephen E., et al. A randomized, double-blind, phase III study comparing multiple doses of tapentadol IR, oxycodone IR, and placebo for postoperative (bunionectomy) pain. *Current medical research and opinion* 25.3 (2009): 765-776.
172. Darchuk, K, et al. Longitudinal Treatment Outcomes for Geriatric Patients with Chronic Non-Cancer Pain at an Interdisciplinary Pain Rehabilitation Program. *Pain Medicine* 2010; 11: 1352–1364 Wiley Periodicals, Inc.
173. Darnall B, et. al., International stakeholder community of pain experts and leaders call for an urgent action on forced opioid tapering *Pain Medicine*, 2019
174. Darnall B, Ziadni M, Stieg R, Mackey I, et. al., Patient-Centered Prescription Opioid Tapering in Community Outpatients with Chronic Pain *JAMA Internal Med.*, 2018
175. Dart RC, et al. Assessment of the abuse of tapentadol immediate release: the first 24 months. *Journal of Opioid Management* 2012; 8:395-402.
176. Dart, R., Diversion and Illicit Sale of Extended Release Tapentadol in the United States, *Pain Medicine* 17:1490 (2016).
177. Dasgupta N, et al. Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. *Pain Med*. 2016 Jan;17(1):85-98

*Lembke Report**Confidential — Subject to Protective Order*

178. Data & Statistics on Sickle Cell Disease, Ctrs. For Disease Control and Prevention, <https://www.cdc.gov/ncbddd/sicklecell/data.html> (last reviewed October 21, 2019).
179. Dave Breitmayer Linkedin Profile, <https://www.linkedin.com/in/davebreitmayer>
180. Davis W, et al. Prescription opioid use, misuse, and diversion among street drug users in New York City. *Drug Alcohol Depend.* 2008; 92:267–276.
181. Davis, M, et al. Prescription Opioid Use among adults with mental health disorders in the United States. *J Am Board Fam Med* 2017;30:407– 417
182. De Vet H, Systematic reviews on the basis of methodological criteria. *Physiotherapy* 1997; 83:284-9.
183. DEA Promoting Pain Relief and Preventing Abuse of Pain Medications: a critical balancing act. A Joint Statement from 21 Health Organizations and the Drug Enforcement Administion, <https://www.deadiversion.usdoj.gov/pubs/advisories/painrelief.pdf>
184. Declaration of Russell K. Portenoy, M.D. in MDL 2804
185. Delgado, et al. National variation in opioid prescribing and risk of prolonged use of opioid-naïve patients treated in the emergency department for ankle sprains. *Ann of Emergency Med*, 12.cl (2018)
186. Dellemijn PLI, et al. Prolonged treatment with transdermal fentanyl in neuropathic pain. *J Pain Symptom Manage* 1998; 16:220–9
187. Demidenko MI, et. al., Suicidal Ideation and Suicidal Self-Directed Violence Following Clinician-Initiated Prescription Opioid Discontinuation Among Long-Term Opioid Users. *General Hospital Psychiatry* 47 (2017) 29-35
188. Deposition Exhibit 26 of Day (Pain Matters. Be the voice tha inspires change)
189. Deposition Exhibit 39 of John Hassler April 4, 2019 (APF, Treatment Options: A Guide for people living with pain) TEVA_MDL_A_01090496-579
190. Deposition Exhibit 6 of John Hassler April 4, 2019 (2005 Actiq marketing Plan) TEVA_CAOC_00759630-713
191. Deposition Exhibit 7 of John Hassler April 4, 2019 (2007 Fentora marketing Plan) TEVA_MDL_A_00364486

*Lembke Report**Confidential — Subject to Protective Order*

192. Deposition Transcript and Exhibits of Bruce M. Bagley May 29, 2019, In Re: National Prescription Opiate Litigation (MDL. No. 2804)
193. Deposition Transcript and Exhibits of Charles Dewildt, February 5, 2020, The People and State of California v. Purdue Pharma L.P., et al., (No. 30-2014-00725287-CU-BT-CXC)
194. Deposition Transcript and Exhibits of Joel R. Saper, M.D., January 11, 2019, In Re: National Prescription Opiate Litigation (MDL No. 2804)
195. Deposition Transcript and Exhibits of John Hassler, April 4, 2019, The People and State of California v. Purdue Pharma L.P., et al., (No. 30-2014-00725287-CU-BT-CXC)
196. Deposition Transcript and Exhibits of John M. Gray, July 30, 2020, Cabell County Commission and City of Huntington, West Virginia v. AmerisourceBergen Drug Corporation, et al. (No. 3:17-01362; 3:17-01665)
197. Deposition Transcript and Exhibits of Kevin Yingling, July 24, 2020, Cabell County Commission and City of Huntington, West Virginia v. AmerisourceBergen Drug Corporation, et al. (No. 3:17-01362; 3:17-01665)
198. Deposition Transcript and Exhibits of Lou Ciampi, February 6, 2020, The People and State of California v. Purdue Pharma L.P., et al., (No. 30-2014-00725287-CU-BT-CXC)
199. deShazo, Richard D. et al. Backstories on the US Opioid Epidemic. Good Intentions Gone Bad, an Industry Gone Rogue, and Watch Dogs Gone to Sleep, *The American Journal of Medicine*, June 2018; 131(6); 595-601
200. Devulder J, Impact of long-term use of opioids on quality of life in patients with chronic nonmalignant pain, *Curr Med Res Opin* 2005;21(10):1555-1568.
201. Deyo, Richard A., et al. Use of prescription opioids before and after an operation for chronic pain (lumbar fusion surgery). *Pain* 159.6 (2018): 1147-1154.
202. *Diagnostic and Statistical Manual of Mental Disorders*. (DSM-5) Washington, DC: American Psychiatric Association; 2013 at p. 541.
203. DiBenedetto DJ, Porter R, Estrada-Lyder MJ, et al. Opioid dose reduction does not worsen pain scores, perceived functional abilities or aberrant drug behaviors in patients on high-dose opioids. *Pain* 2014;15 (3):511, A165.
204. DiJulio, B., et al. Post Kaiser Long-Term Prescription Opioid Painkiller Users Poll, Oct. 3-Nov. 9, 2016. The Washington Post; https://www.washingtonpost.com/page/2010-2019/WashingtonPost/2016/12/09/National-Politics/Polling/release_455.xml?uuid=3JgevL47Eeaueb7HLTT4yQ

*Lembke Report**Confidential — Subject to Protective Order*

205. Dole VP, et al. Heroin addiction—a metabolic disease. *Arch Intern Med.* 1967; 120(1):19–24.
206. Donohue JM, Kennedy JN, Seymour CW, Girard TD, Lo-Ciganic WH, Kim CH, Marroquin OC, Moyo P, Chang CH, Angus DC. Patterns of Opioid Administration Among Opioid-Naive Inpatients and Associations With Postdischarge Opioid Use: A Cohort Study. *Ann Intern Med.* 2019
207. Doquang-Cantagrel N, et al. Tolerability and efficacy of opioids in chronic nonmalignant pain. *Addiction* 1991; 722:129.
208. Dowell D, et al. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA - J Am Med Assoc.* 2016; 315(15):1624-1645. doi:10.1001/jama.2016.1464
209. Dowell D, Jones C, Compton W. HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics. YS Department of Health and Human Services (Sept. 2019)
210. Dowell, Deborah, Tamara Haegerich, and Roger Chou. No shortcuts to safer opioid prescribing. *New England Journal of Medicine* 380.24 (2019): 2285-2287.
211. Dowell, et al., Patient-Centered Reduction or Discontinuation of Long-Term Opioid Analgesics. *JAMA.* 2019;322(19):1855-1856. doi:10.1001/jama.2019.16409
212. Drossman DA, Morris CB, Edwards H, et al. Diagnosis, characterization, and 3-month outcome after detoxification of 39 patients with narcotic bowel syndrome. *Am J Gastroenterol* 2012;107 (9):1426–40.
213. *Drug Abuse in Egypt: A pill for work and play*, The Economist, April 18, 2015.
214. Dunbar SA, et al. Chronic opioid therapy for nonmalignant pain in patients with a history of substance abuse: Report of 20 cases. *J Pain Symptom Manage* 1996; 11:163–71
215. Dunn, Kate, et al. Opioid Prescriptions for Chronic Pain and Overdose: A Cohort Study, *Annals of Internal Medicine* 2010; 152(2):85-92
216. Durand, Zoe, et al. Prevalence and Risk Factors Associated With Long-term Opioid Use After Injury Among Previously Opioid-Free Workers. *JAMA network open* 2.7 (2019): e197222-e197222.
217. Dyer, Owen. "WHO retracts opioid guidelines after accepting that industry had an influence." *BMJ* (2020).
218. Ed Hazewski Linkedin Profile, <https://www.linkedin.com/in/edwardhazewski>

*Lembke Report**Confidential — Subject to Protective Order*

219. Edelman EJ, et al. Association of Prescribed Opioids with Increased Risk of Community-Acquired Pneumonia among Patients with and Without HIV. *JAMA Intern Med.* 2019; 179(3):297-304. doi:10.1001/jamainternmed.2018.6101
220. Edlund MJ, et al. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? *Pain Med* 2007;8:647–56.
221. Edlund MJ, et al. Patterns of opioid use for chronic noncancer pain in the Veterans Health Administration from 2009 to 2011. *J.Pain.* 2014 Nov;1 55(11):2337-43. doi: 10.1016/j.pain.2014.08.033. Epub 2014 Aug 29.
222. Edlund MJ, et al. Risks of opioid abuse and dependence among recipients of chronic opioid therapy results from the TROUP study. *Drug Alcohol Depend* 2010; 112:90–8.
223. Edlund MJ, et al. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *Clin J Pain.* 2014 Jul; 30(7):557-64. doi: 10.1097/AJP.000000000000021.PMID: 24281273
224. Egan K, Katon W. Chronic Pain: Lifetime Psychiatric Diagnoses and Family History. *Am J Psychiatry.* 1985;(October):1156-1160.
225. Egilman D, et al. The Marketing of OxyContin: a cautionary tale. *Indian Journal of Medical Ethics.* 4(3): 2019
226. Eisenberg, Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials, *JAMA* 2005; 293(24):3043-52.
227. Eisenberg, Opioids for neuropathic pain, *Cochrane Database of Systemic Reviews* 2006; 3:CD006146.
228. Eissenberg JC, Aurora R. Pharmacogenomics: What the Doctor Ordered? *Missouri Medicine* (2019)
229. Elander J. Understanding the causes of problematic pain management in sickle cell disease: evidence that pseudoaddiction plays a more important role than genuine analgesic dependence. *J Pain & Symptom Manage* 2004;27(2)156-169.
230. Els, et al., High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev.* 2017 Oct; 2017(10): CD012299
231. ErikSEN, Jørgen, et al. Critical issues on opioids in chronic non-cancer pain: An epidemiological study, *Journal of the International Association for the Study of Pain* 2006; 125(1-2):172-9

*Lembke Report**Confidential — Subject to Protective Order*

232. Eriksson, R. et al. Discrepancies in listed adverse drug reactions in pharmaceutical product information supplied by the regulatory authorities in Denmark and the USA. *Pharmacol Res Perspect.* 2014; 2(3):1-10. doi:10.1002/prp2.38
233. Evans, P.J.D. Narcotic addiction in patients with chronic pain, *Anesthesia*, 1981, Vol. 36, 597-602
234. Faria, J., et al. Comparative pharmacology and toxicology of tramadol and tapentadol. *European Journal of Pain* 22.5 (2018): 827-844.
235. Fauber J, FDA and pharma: emails raise pay-for-play concerns. *Sentinel/MedPage Today.* <http://www.medpagetoday.com/PainManagement/PainManagement/42103>.
236. Fauber, John, Past investigations exposed links between drug companies, push for use of opioids, *Milwaukee Journal Sentinel*, 2018
237. FDA FDA Identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual individualized tapering. 4/9/2019 fda.gov
238. FDA News Release: FDA Requiring Labeling Changes for Opioid Pain Medicines, Opioid Use Disorder Medicines Regarding Naloxone, July 23, 2020, <https://www.fda.gov/news-events/press-announcements/fda-requiring-labeling-changes-opioid-pain-medicines-opioid-use-disorder-medicines-regarding>
239. FDA, MEDWATCH report: USA-2002-0003578, FDA
240. FDA, MEDWATCH report: USA-2002-0003579, FDA
241. FDA, MEDWATCH report: USA-2002-0003587, FDA
242. FDA, MEDWATCH report: USA-2002-0003667, FDA
243. FDA, MEDWATCH report: USA-2003-0009708, FDA
244. FDA, MEDWATCH report: USA-2003-0009825, FDA
245. FDA, MEDWATCH report: USA-2003-0009846, FDA
246. FDA, MEDWATCH report: USA-2003-0009896, FDA
247. FDA-CDER Letter to Janssen (August 1, 2003)
248. FDA-CDER. NDA 20-281 File. (March 3, 1995), https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020281Orig1s000rev.pdf.

*Lembke Report**Confidential — Subject to Protective Order*

249. FDA-CDER. NDA 20-281 File. (March 3, 1995).
https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020281Orig1s000rev.pdf
250. Federation of State Medical Board's Model Guidelines on the Use of Controlled Substances for Pain Management (2004),
http://www.fsmb.org/Policy%20Documents%20and%20White%20Papers/2004_model_pain_policy.asp
251. Federation of State Medical Boards. *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain* (May 2, 1988),
https://painpolicy.iu.edu/sites/default/files/sites/www.painpolicy.wisc.edu/files/model_0.pdf.
252. Fenton, Joshua J., et al. Trends and Rapidity of Dose Tapering Among Patients Prescribed Long-term Opioid Therapy, 2008-2017. JAMA network open 2.11 (2019): e1916271-e1916271.
253. Ferrari A. Need for analgesics/drugs of abuse: a comparison between headache patients and addicts by the Leeds Dependence Questionnaire (LDQ), Cephalgia 2006;26(2):187-93.
254. Finkelstein, A. et al. What Drives Prescription Opioid Abuse? Evidence from Midration. Stanford. SIEPR. August, 2018.
255. Finney, Fred T., et al. Rate of opioid prescriptions for patients with acute ankle sprain. Annals of internal medicine (2019).
256. Fishbain DA, et al. Does Opioid Tapering in Chronic Pain Patients Result in Improved Pain or Same Pain vs Increased Pain at Taper Completion? A Structured Evidence-Based Systematic Review. Pain Med. 2018. doi:10.1093/pmj/nyz231
257. Fishbain DA, et al. Drug Abuse, Dependence, and Addiction in Chronic Pain Patients. The Clinical Journal of Pain 1992;8:77-85
258. Fishbain DA. Medico-Legal Rounds: Medico-Legal Issues and Breaches of 'Standards of Medical Care' in Opioid Tapering for Alleged Opioid Addiction. Pain Medicine 3(2) 2002. 135-142
259. Fishbain, DA, Chronic pain and addiction, Chapter 10 in Weiner's Pain Management, a Practical Guide for Clinicians, 7th Edition, Eds. Boswell MV, Cole BE, CRC Press Boca Raton, Florida, 2006;117-139.
260. Fishbain, DA, et al. What percentage of Chronic Nonmalignant Patients Exposed to Chronic Opioid Analgesic Therapy Develop Abuse/Addiction and/or Aberrant Drug-

- Related Behaviors? A Structured Evidence-based Review. *Pain Medicine*. Vol 9.4 (2008): 444-459 with Appendices.
261. Fishman SM. Responsible opioid prescribing: A physician's guide. Washington, DC: Waterford Life Sciences; 2007
 262. Fleming MF, et al. Reported lifetime aberrant drug-taking behaviors are predictive of current substance use and mental health problems in primary care patients. *Pain Med* 2008; 9:1098–106.
 263. Fleming MF, et al. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain* 2007; 8:573–82.
 264. Foley KM, et al. A true believer's flawed analysis. *Arch Intern Med*. 2011. doi:10.1001/archinternmed.2011.166
 265. Food and Drug Administration Center for Drug Evaluation and Research, Application Number: 22-304 (November 4, 2008), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_OtherR.pdf, at p. 2.
 266. Fortenberry M, et al. The use of codeine and tramadol in the pediatric populations – what is the verdict now? *J Pediatr Health Care* 2019;33:117-123, at p. 117
 267. Foster Care Placements Report November 30th 2019
 268. Fournier J-P, et. al. Tramadol use and the risk of hospitalization for hypoglycemia in patients with noncancer pain. *JAMA Intern Med*. 2015;175(2):186-193, at p. 186.
 269. France RD, et al. Long-term use of narcotic analgesics in chronic pain. *Soc Sci Med* 1984; 19: 1379–82
 270. Frank JW, et al. Patient outcomes in dose reduction or discontinuation of long- term opioid therapy: A systematic review. *Ann Intern Med*. 2017; 167(3):181- 191. doi:10.7326/M17-0598
 271. Franklin GM, et al. Early opioid prescription and subsequent disability among workers with back injuries. *SPINE*. 2008; 33(2): 199-204.
 272. Frankt AB, et al. Protection or harm? Suppressing substance use data. *N Engl J Med*. 2015 May 14; 372(20):1879–1881.

*Lembke Report**Confidential — Subject to Protective Order*

273. Frasco PE, et al. The impact of the joint commission for accreditation of healthcare organizations pain initiative on perioperative opiate consumption and recovery room length of stay. *Anesth Analg.* 2005; 100:162–168.
274. Frieden TR, et al. Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline. *N Engl J Med.* 2016. doi:10.1056/nejmp1515917
275. Frolich, M. et al. Opioid overdose in a patient using fentanyl patch during treatment with a warming blanket, *Anesth Analg* 2001;93:647–8
276. FSMB, Model Guidelines for the Use of Controlled Substances for the Treatment of Pain (May 2, 1988),
https://painpolicy.iu.edu/sites/default/files/sites/www.painpolicy.wisc.edu/files/model_0.pdf.
277. Furlan A, et al. Opioids for chronic noncancer pain: A metaanalysis of effectiveness and side effects. *CMAJ* 2006; 174:1589–94.
278. Furlan AD, et al. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Res Manag.* 2011; 16(5):337-351. doi:10.1155/2011/465281
279. Galer, Bradley, et al. Defeat Chronic Pain Now! Groundbreaking Strategies for eliminating the pain of arthritis back and neck conditions, migraines, diabetic neuropathy, and chronic illness, Fair Winds Press, pages 155-77
280. GAO, Prescription OxyContin abuse and diversion and efforts to address the problem. *J Pain Palliat Care Pharmacother.* 2003;18(3):109–113.
281. Garland EL, et al. Adverse Childhood Experiences Predict Autonomic Indices of Emotion Dysregulation and Negative Emotional Cue-Elicited Craving Among Female Opioid-Treated Chronic Pain Patients. *Development and Psychopathology* (2019)
282. General Assembly of the State of Ohio, An Act. Sections 4731.052 and 4731.283 of the Revised Code regarding the authority of physicians to prescribe, dispense, and administer dangerous drugs for management of intractable pain. Ohio Intractable Pain Law. Substitute House Bill Number 187. General Assembly of the State of Ohio
283. George O, et al. Allostasis and addiction: role of the dopamine and corticotropin-releasing factor systems. *Physiol Behav.* 2012; 106(1):58–64.
284. Ghertner, Robin. US county prevalence of retail prescription opioid sales and opioid-related hospitalizations from 2011 to 2014. *Drug and alcohol dependence* 194 (2019): 330-335.

*Lembke Report**Confidential — Subject to Protective Order*

285. Gil, Joseph A., et al. Risk of prolonged opioid use among opioid-naïve patients after common shoulder arthroscopy procedures. *The American journal of sports medicine* 47.5 (2019): 1043-1050.
286. Gilson AM. The concept of addiction in law and regulatory policy: A critical review. *Clinical Journal of Pain*. 2010; 26(1):70-77
287. Gilson, et al. The Evolution of the Opiate/Opioid Crisis in Cuyahoga County. *Acad. Forensic Pathology*, 7:41-49 (2017)
288. Gilson, R. et al. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997-2002. *J Pain Symptom Manage*. 2004 Aug;28(2):176-88
289. Gimpel JS, Controlled-release oxycodone for pain in diabetic neuropathy. A randomized controlled trial, *Neurology* 2003; 60.
290. Glanz - Association Between Opioid Dose Variability and Opioid Overdose Among Adults Prescribed Long-term Opioid Therapy. *JAMA Network Open*. 2019;2(4):e192613. doi:10.1001/jamanetworkopen.2019.2613
291. Goesling J., Ilgen M. (2019) Effective Opioid Analgesic Alternatives and Approaches to Pain Management. In: Kelly J., Wakeman S. (eds) Treating Opioid Addiction. Current Clinical Psychiatry. Humana, Cham
292. Goesling, Jenna, et al. Opioid cessation and chronic pain: perspectives of former opioid users. *Pain* 160.5 (2019): 1131-1145.
293. Goesling, Jenna, et al. Trends and predictors of opioid use following total knee and total hip arthroplasty. *Pain* 157.6 (2016): 1259.
294. Gomes T, Juurlink D et al. Geographic Variation in Opioid Prescribing and Opioid-Related Mortality in Ontario. *Healthcare Quarterly*, 14: 22-24 (2011)
295. Gomes T. et al. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*. 2011 Apr 11;171(7):686-91. doi: 10.1001/archinternmed.2011.117.
296. Grau LE, et al. Illicit use of opioids: is OxyContin a gateway drug?, *Am J Addict* 2007;16:166-173
297. Graves v. Purdue Pharma Ltd, et al. Notice of Defendants' Designation of Expert Witnesses. Civil Action 2:07cv107-MPM-SAA (USDC NMS)

*Lembke Report**Confidential — Subject to Protective Order*

298. Graves v. Purdue Pharma Ltd, et al. Rule 26(a)(2) Disclosure of David A. Fishbain, MD, Civil Action 2:07cv107-MPM-SAA (USDC NMS)
299. Greene, et al. Pseudoaddiction: Fact or Fiction? An Investigation of the Medical Literature, *Curr Addict Rep.* 2015; 2(4): 310–317.
300. Grigoras CA, Karanika S, et al. Correlation of Opioid Mortality with Prescriptions and Social Determinants: A cross-sectional study of medicare enrollees. *Drugs* (2018) 78:111-121
301. Gu Q, et al. Prescription drug use continues to increase: U.S. prescription drug data for 2007–2008. *NCHS Data Brief.* 2010; (42):1–8.
302. Gudin J, et al. Long-term safety and tolerability of NKTR-181 in patients with moderate to severe chronic low back pain or chronic noncancer pain: A phase 3 multicenter, open-label, 52-week study (SUMMIT-08 LTS) *Pain Medicine* (2019)
303. Guy GP, Zhang Z, Schieber LZ. County-Level Opioid Prescribing in the United States, 2015 and 2017 Supplementary Online Content *JAMA Internal Medicine* April 2019 Volume 179, Number 4
304. Guy GP, Zhang Z, Schieber LZ. County-Level Opioid Prescribing in the United States, 2015 and 2017. *JAMA Internal Medicine* April 2019 Volume 179, Number 4
305. H. Siegal, et al., Probable Relationship Between Opioid Abuse and Heroin Use, *A. Fam. Physician* 67:942 (2003)
306. Haddox, J. D. et al. The use of opioids for the treatment of chronic pain: a consensus statement from the American Academy of Pain Medicine and the American Pain Society. *APS News* 77-79. *Clin J Pain.* 1997; 13(1).
307. Hadland S, et al. Industry Payments to Physicians for Opioid Products, 2013-2015. *Am J Public Health.* 2017; 107:1493-1495.
308. Hadland, Scott E. et al. Association of Pharmaceutical Industry Marketing of Opioid Products to Physicians With Subsequent Opioid Prescribing, *JAMA Intern Med.* 2018; 178(6):861-863.
309. Hale, Martin, et al. Efficacy and safety of Opana ER for Relief of Moderate to Severe Chronic Low Back Pain in Opioid-Experienced patients: a 12-week, randomized, double-blinding, placebo-controlled study. *The Journal of Pain*, Vol 8, No 2 (February), 2007: pp 175-184

Lembke Report

Confidential — Subject to Protective Order

- 310. Hale, Martin, et al. Tolerability of tapentadol immediate release in patients with lower back pain or osteoarthritis of the hip or knee over 90 days: a randomized, double-blind study. *Current medical research and opinion* 25.5 (2009): 1095-1104.
- 311. Hall AJ, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA*. 2008; 300(22):2613–2620.
- 312. Hall ES *et al.* Developmental disorders and medical complications among infants with subclinical intrauterine opioid exposures. *Population Health Management*. 2019;22:19-24, at p. 21.
- 313. Hall, W. What are the policy lessons of National Alcohol Prohibition in the U.S. 1920-1933?, *Addiction*, 105m 1164-73 (2009)
- 314. Han B, et al. Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003–2013. *JAMA*. 2015; 314:1468–1478.
- 315. Han B, et al. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Annals of internal medicine*. 2017;167(5):293-301. Epub 2017/08/02. doi: 10.7326/m17-0865. PubMed PMID: 28761945
- 316. Harati Y, Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy, *Neurology* 1998;50(6):1842-1846.
- 317. Harbaugh, Calista M., et al. Persistent opioid use among pediatric patients after surgery. *Pediatrics* 141.1 (2018): e20172439.
- 318. Harris v Purdue Pharma et al., No. C-1-01-428, 2004 WL 4012101 (S.D. Ohio 2004)
- 319. Harrison TK, et al. Perioperative Considerations for the Patient with Opioid Use Disorder on Buprenorphine, Methadone, or Naltrexone Maintenance Therapy. *Anesthesiol Clin*. 2018;36(3):345-359. doi:10.1016/j.anclin.2018.04.002
- 320. Hartrick, Craig, et al. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active-and placebo-controlled study. *Clinical therapeutics* 31.2 (2009): 260-271.
- 321. Hasin DS, O'Brien CP *et al.* DSM-5 Criteria for Substance Use Disorders: recommendations and rationale. *Am J Psychiatry* 2013;170(8):834-851. at p.2, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3767415/pdf/nihms515995.pdf>,
- 322. Hassenbusch, S, et al. Long Term Intraspinal Infusions of Opioids in the Treatment of Neuropathic Pain. *Journal of Pain and Symptom Management*. 1995;10:527-543

323. Häuser W, et al. Long-term opioid therapy in chronic noncancer pain. A systematic review and meta-analysis of efficacy, tolerability and safety in open-label extension trials with study duration of at least 26 weeks. *Schmerz.* 2015 Feb; 29(1):96-108. doi: 10.1007/s00482-014-1452-0.
324. Häuser W, et al. The opioid epidemic and the long-term opioid therapy for chronic noncancer pain revisited: a transatlantic perspective. *Pain Manag.* 2016. doi:10.2217/pmt.16.5
325. Hauser, W., et al. Meta-analysis of Opioids for Chronic Pain. *JAMA* May 21, 2019 Volume 321, Number 19. 1934-36
326. Havens JR, et al. Prescription opiate misuse among rural stimulant users in a multistate community-based study. *Am J Drug Alcohol Abuse* 2009; 35:18-23
327. Hayes C. et al. Evaluation of opioid use among patients with back disorders and arthritis. Springer Link. *Quality of Life Research.* July 23, 2018.
328. Haythornthwaite JA, Outcome of chronic opioid therapy for non-cancer pain. *Journal of Pain and Symptom Management* 1998; 15 (3)
329. Health Affairs Blog, The Addiction Recovery Medical Home As An Alternative Payment Model, December 12, 2018. DOI: 10.1377/hblog20181211.111071. Heal Aff Blog. doi: 10.1377/hblog20181211.111071
330. Health Professionals for Patients in Pain (HP3) Professionals Call on the CDC to Address Misapplication of its Guideline on Opioids for Chronic Pain through Public Clarification and Impact Evaluation Letter to the CDC March 6th 2019
331. Healthcare Distribution Management Association. Reporting Suspicious Orders and Preventing Diversion of Controlled Substances.
332. Heaton, Cheryl, Robert Pack, and Sandro Galea. The Opioid Crisis, Corporate Responsibility, and Lessons From the Tobacco Master Settlement Agreement. *Jama* 322.21 (2019): 2071-2072.
333. Hedberg, Katrina, et al. Integrating Public Health and Health Care Strategies to Address the Opioid Epidemic: The Oregon Health Authority's Opioid Initiative. *Journal of Public Health Management and Practice* 25.3 (2019): 214-220.
334. Heit, Howard A., and Douglas L. Gourlay. "DSM-V and the definitions: time to get it right." *Pain medicine* 10.5 (2009): 784-786.

335. Heyward, James, et al. "Evaluation of the Extended-Release/Long-Acting Opioid Prescribing Risk Evaluation and Mitigation Strategy Program by the US Food and Drug Administration: A Review." *JAMA Internal Medicine* (2019).
336. Higgins, C. et al. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis, *British Journal of Anesthesia*, 120 (6): 1335-44 (2018)
337. Higham, S. 76 billion opioid pills: Newly released federal data unmasks the epidemic. *Washington Post* (2019), https://www.washingtonpost.com/investigations/76-billion-opioid-pills-newly-released-federal-data-unmasks-the-epidemic/2019/07/16/5f29fd62-a73e-11e9-86dd-d7f0e60391e9_story.html
338. Hinther, Ashley, et al. Chronic Postoperative Opioid Use: A Systematic Review. *World journal of surgery* (2019): 1-11.
339. Hoaglin, D. Meta-analysis of Opioids for Chronic Pain. *JAMA* May 21, 2019 Volume 321, Number 19. 1934-36
340. Hobbs, Typer, Eliminating Opioid Use in the Treatment of Chronic Lower-Back Pain, All Student Publications, 2018; 229.
341. Hoffer L, Modelling Local Heroin Markets. Case Western Reserve University (2016)
342. Hoffer, Lee. Modeling Local Heroin Markets. Dept of Anthropology. Case Western Reserve University. Task Force 2016.
343. Højsted J, et al. Classification and identification of opioid addiction in chronic pain patients. *Eur J Pain* 2010; 14:1014–20.
344. Holte, A., et al. Restrictive Opioid Prescribing Protocols Following Total Hip Arthroplasty and Total Knee Arthroplasty Are Safe and Effective. *The Journal of Arthroplasty* xxx (2019) 1-5
345. Hoogendoorn WE, Systematic review of psychosocial factors at work and private life as risk factors for back pain, *Spine* 2000;25:2114-25.
346. Hooten WM, Mantilla CB, Sandroni P, Townsend CO. Associations between heat pain perception and opioid dose among patients with chronic pain undergoing opioid tapering. *Pain Med* 2010;11 (11):1587–98.
347. Hooten WM, Warner D. Varenicline for opioid withdrawal in patients with chronic pain; a randomized, single-blinded, placebo controlled pilot trial. *Addict Behav* 2015;42:69–72.

*Lembke Report**Confidential — Subject to Protective Order*

348. How to Taper Patients Off of Chronic Opioid Therapy, Stanford University School of Medicine, <https://med.stanford.edu/cme/courses/online/opioid-taper.html>.
349. Howard Fields Report 02/03/2020 In re Opioid Litigation, Case No. 400000/2017
350. Howard R, et al. Association of Opioid Prescribing with Opioid Consumption after Surgery in Michigan. *JAMA Surgery*. 2018.
351. Howard, Ryan, et al. Reduction in opioid prescribing through evidence-based prescribing guidelines. *JAMA surgery* 153.3 (2018): 285-287.
352. Hruschak V, Cochran G, Wasan A. Psychosocial Interventions for Chronic Pain and Comorbid Prescription Opioid Use Disorders: a narrative review of the literature. *Journal of Opioid Management* (2018)
353. HSS, Addressing prescription drug abuse in US. Current Activities and Future Opportunities, Behavioral Health Coordinating Committee. Prescription Drug Abuse Subcommittee U.S. Department of Health and Human Services. 200 Independence Avenue SW. Washington, DC 20201
354. Human Rights Watch - Not Allowed to Be Compassionate - The Overdose Crisis <https://www.hrw.org/report/2018/12/18/not-allowed-be-compassionate/chronic-pain-overdose-crisis-and-unintended-harms-us>
355. Humphreys K. Americans use far more opioids than anyone else in the world. *The Washington Post*. https://www.washingtonpost.com/news/wonk/wp/2017/03/15/americans-use-far-more-opioids-than-anyone-else-in-the-world/?utm_term=.46bc462abe56. Published 2017.
356. Humphreys, Keith. "Avoiding globalisation of the prescription opioid epidemic." *The Lancet* 390.10093 (2017): 437-439.
357. Hunt S. Amending the Federal Controlled Substances Act: fostering public health innovation at the local level. *Roosevelt Review* (2019)
358. HUNT_00009992 [Portal to Recovery - National RX Drug Abuse and Heroin Summit Presentation]
359. Huse E, The effect of opioids on phantom limb pain and cortical reorganization, *Pain* 2001; 90: 47-55.
360. Ilgen MA, et al. Opioid Dose and Risk of Suicide. *Pain*. 2016 May ; 157(5): 1079–1084

*Lembke Report**Confidential — Subject to Protective Order*

361. Inciardi JA, et al., Prescription Opioid Abuse and Diversion in an Urban Community: The Results of an Ultra-Rapid Assessment. *Pain Medicine*. 2009;10:537-548, at p. 544.
362. Institute of Medicine Committee to advise Public Health Service on Clinical Practice, Clinical Practice Guidelines Directions for a new program. Washington DC: National Academy Press 1990.
363. International Narcotics Control Board, Narcotic Drugs Technical Report 2016. See https://www.incb.org/incb/en/narcotic-drugs/Technical_Reports/2016/narcotic-drugs-technical-report-2016.html
364. International Stakeholder Community of Pain Experts and Leaders Call for an Urgent Action on Forced Opioid Tapering, *Pain Medicine* 2019; 20: 429–433
365. Islam M, Wollersheim D. A Comparison of Opioids and Benzodiazepines Dispensing in Australia. *Plos One* (2019)
366. Ives TJ, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res* 2006;6:46.
367. Izrailyan I, et al. Risk factors for cardiopulmonary and respiratory arrest in medical and surgical hospital patients on opioid analgesics and sedatives. *PLoS One*. 2018 Mar 22; 13(3):e0194553. doi: 10.1371/journal.pone.0194553. eCollection 2018
368. Jadad, et al. Morphine responsiveness of chronic pain: double-blind randomised crossover study with patient-controlled analgesia, *The Lancet*. V 339(8806) 1367- 71
369. Jaffe J. Opiates: clinical aspects. In Lowenson J, Ruiz P, Mullman R (Eds). *Substance abuse, a comprehensive text* Baltimore: Williams & Wilkins 1992:186- 194.
370. Jalal H, et al. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science* (80-). 2018. doi:10.1126/science.aau1184
371. James L. Madara, MD (AMA) to Deborah Dowell, MD (CDC), Re: Docket No. CDC-2020-0029, June 16, 2020, <https://searchlf.ama-assn.org/undefined/documentDownload?uri=%2Funstructured%2Fbinary%2Fletter%2FLETTERS%2F2020-6-16-Letter-to-Dowell-re-Opioid-Rx-Guideline.pdf>.
372. James L. Madara, MD (AMA) to Deborah Dowell, MD (CDC), Re: Docket No. CDC-2020-0029, June 16, 2020, <https://searchlf.ama-assn.org/undefined/documentDownload?uri=%2Funstructured%2Fbinary%2Fletter%2FLETTERS%2F2020-6-16-Letter-to-Dowell-re-Opioid-Rx-Guideline.pdf>.

*Lembke Report**Confidential — Subject to Protective Order*

373. Jamison RN, et al. Do pain patients at high risk for substance misuse experience more pain? A longitudinal outcomes study. *Pain Med* 2009;10:1084–94
374. Jamison RN, et al. Gender differences in risk factors for aberrant prescription opioid use. *J Pain* 2010; 11:312–20.
375. Jamison RN, et al. Opioid therapy for chronic non-cancer back pain. A randomized prospective study. *Spine* 1998; 23: 2591–600
376. Jeffery MM, et al. Trends in opioid use in commercially insured and Medicare Advantage populations in 2007-16: retrospective cohort study. *Bmj*. 2018; 362:k2833. doi:10.1136/bmj.k2833
377. Jeffery, Molly Moore, et al. "Assessment of Potentially Inappropriate Prescribing of Opioid Analgesics Requiring Prior Opioid Tolerance." *JAMA network open* 3.4 (2020): e202875-e202875.
378. Johnson H, et al. Decline in drug overdose deaths after state policy changes - Florida, 2010-2012. *MMWR Morb Mortal Wkly Rep*. 2014 Jul 4;63(26):569-74
379. Johnson, Shepard P., et al. Risk of prolonged opioid use among opioid-naïve patients following common hand surgery procedures. *The Journal of hand surgery* 41.10 (2016): 947-957.
380. Jones CM, et al. Vital Signs: Demographic and Substance Use Trends Among Heroin Users - United States, 2002-2013. *MMWR Morb Mortal Wkly Rep*. 2015 Jul 10;64(26):719-25. PMID:26158353
381. Jones JD, et al. Comer SD. Oxycodone abuse in New York City: characteristics of intravenous and intranasal users. *Am J Addict* 2011;20:190-195
382. Jones, Christopher M. et al. Changes in Synthetic Opioid Involvement in Drug Overdose Deaths, *JAMA*, 2018; 319; 17
383. Joranson, DE, et al. Trends in Medical Use and Abuse of Opioid Analgesics. *JAMA* April 5, 2000—Vol 283, No. 13. 1710-14
384. Judgement After Non-Jury Trial in State of Oklahoma ex rel Hunter v Purdue et al. No. CJ-2017-816
385. Julie Eddy Linkedin Profile, <https://www.linkedin.com/in/julie-eddy-458b118>
386. Just JM, et al. Opioid Use Disorder in Chronic Noncancer Pain in Germany: a cross-sectional study. *BMJ Open* (2019)

387. Justin Morgenstern " Don't prescribe Tramadol" Published May 13, 2019-Updated November 17, 2019 <https://first10em.com/tramadol/>
388. Justin Scheck, *Tramadol: The opioid crisis for the rest of the world*, Wall St. J., Oct. 19, 2016.
389. Juurlink MD. Rethinking doing well on chronic opioid therapy. CMAJ 2017 October 2; 189:E1222-3. doi: 10.1503/cmaj.170628.
390. Juurlink MD., et al. Dependence and Addiction During Chronic Opioid Therapy. J. Med. Toxicol. (2012) 8:393–399. DOI 10.1007/s13181-012-0269-4
391. Kalkman, Gerard Arnoldus, et al. "Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-source database study." The Lancet Public Health 4.10 (2019): e498-e505.
392. Kalso E, Opioids in chronic non-cancer pain: systematic review of efficacy and safety, Pain 2004; 112(3):372-80.
393. Katon, W. et al. Chronic Pain: Lifetime Psychiatric Diagnoses and Family History, Am J Psychiatry 1985; 142:1156-60
394. Katz NP, et al. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesth Analg 2003; 97:1097–102.
395. Katz NP, Role of urine toxicology testing in the management of chronic opioid therapy. Clin J Pain 2002; 18(4 Suppl):S76-82.
396. Katz, J., et al., In Shadow of Pandemic, U.S. Drug Overdose Deaths Resurge to Record. The New York Times, July 15, 2020.
<https://www.nytimes.com/interactive/2020/07/15/upshot/drug-overdose-deaths.html>
397. Katz, NP, et al. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naïve patients with chronic low back pain. Current Medical Research and Opinion, 23:1, 117- 128, DOI: 10.1185/030079906X162692
398. Kauer JA, et al. Synaptic plasticity and addiction. Nat Rev Neurosci. 2007; 8(11):844–858.
399. Kaye A, et al. No Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1.Title. Pain Physician J. 2017

*Lembke Report**Confidential — Subject to Protective Order*

400. Kaye AD, et al. Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse (Part 2). *Pain Physician*. 2017 Feb; 20(2S):S111-S133.
401. Kaye, Alan David, et al. Novel pharmacological nonopioid therapies in chronic pain. *Current pain and headache reports* 22.4 (2018): 31.
402. Kell MJ, et al. Methadone prophylaxis of intractable headaches: Pain control and serum opioid levels. *AJPM* 1993; b3:7–14
403. Kell MJ, Long-term methadone maintenance for intractable, nonmalignant pain: Pain control and plasma opioid levels. *AJPM* 1994; 4:10–6
404. Kell, M. Monitoring compliance with OxyContin Rx in 14,712 patients treated in 127 outpatient pain centers. *Pain Med* 2005; 6 (2).
405. Kertesz SG, Manhapra A, The Drive to Taper Opioids: Mind the Evidence and the Ethics. *Spinal Cord Series and Cases* (2018) 4:64
406. Kertesz, Stefan G., et al. Opioid discontinuation as an institutional mandate: Questions and answers on why we wrote to the Centers for Disease Control and Prevention. (2019): 1-3.
407. Kevin Kreutzer Linkedin Profile, <https://www.linkedin.com/in/kevin-kreutzer-b1763512>
408. Khan, Nazleen F., et al. Association of Opioid Overdose With Opioid Prescriptions to Family Members. *JAMA internal medicine* (2019).
409. Kheirabadi G, et al. Gabapentin, Pregabalin and Placebo in Reducing Opioid Withdrawal Symptoms in Opioid-Dependent Individuals: a randomized-controlled trial. *Addict Disord Their Treatment* (2018)
410. Khosla N, et al. Correlates of non-medical prescription drug use among a cohort of injection drug users in Baltimore City. *Addict Behav* 2011;36:1282-1287
411. Kiang MV, et al. Opioid prescribing patterns among medical providers in the United States, 2003-17: retrospective, observational study. *BMJ* 2020
412. Kidner CL, Mayer TG, Gatchel RJ. Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. *J Bone Joint Surg Am* 2009;91(4):919–27
413. Kirsh K. Abuse and addiction issues in medically ill patients with pain: attempts at clarification of terms and empirical study, *Clin J Pain* 2002; 18:S52-S60.

*Lembke Report**Confidential — Subject to Protective Order*

414. Kjaersgaard-Andersen P, Codeine plus paracetamol versus paracetamol in longer- term treatment of chronic pain due to osteoarthritis of the hip. A randomized, double-blind, multi-centre study, *Pain* 1990; 43: 309-318.
415. Klimas, et al., Strategies to Identify Patient Risks of Prescription Opioid Addiction When Initiating Opioids for Pain: A Systematic Review. *JAMA Netw Open*. 2019;2(5):e193365. doi:10.1001/jamanetworkopen.2019.3365.
416. Kocher R, et al. Hospitals' Race to Employ Physicians — The Logic Behind a Money Losing Proposition. *NEJM*. 2011;1790-1793
417. Kolodny, A. Live interview with Dr. Russel Portenoy. Physicians for Responsible Opioid Prescribing. <https://www.youtube.com/watch?v=DgyuBWN9D4w>. Accessed September 2, 2015.
418. Kolodny, A. The opioid epidemic in 6 charts, *The Conversation*, 2018
419. Koob GF, et al. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010; 35:217-238. doi:10.1038/npp.2010.4
420. Kornfield, M. Drug distributor employees emailed a parody song about "pillbillies" documents show. *Washington Post*. May 23, 2020. at https://www.washingtonpost.com/national/drug-distributor-employees-emailed-a-parody-song-about-pillbillies-documents-show/2020/05/23/823f148e-9cf4-11ea-a2b3-5c3f2d1586df_story.html
421. Kostopoulos D. Non-prescription medication providers fight opioid crisis with use of diagnostic testing. *Journal of Bodywork & Movement Therapies* (2019)
422. Krans, Elizabeth E., and Stephen W. Patrick. Opioid use disorder in pregnancy: health policy and practice in the midst of an epidemic. *Obstetrics and gynecology* 128.1 (2016): 4.
423. Krebs EE et al., In reply: opioids vs nonopioids for chronic back, hip or knee pain. *JAMA*. 2018;305(5): 508-509 at p. 509.
424. Krebs EE, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. *JAMA*. 2018 Mar 6;319(9):872-882. doi:10.1001/jama.2018.0899.
425. Krebs EE, Gravely A, Nugent S, et al. Supplementary Online Content - Effect of opioid vs non-opioid medications on pain-related function in patients with chronic back pain or

hip or knee osteoarthritis pain: the SPACE randomized clinical trial. JAMA.
doi:10.1001/jama.2018.0899

426. Kroenke, Kurt, et al. Challenges with implementing the centers for disease control and prevention opioid guideline: a consensus panel report. Pain Medicine 20.4 (2019): 724-735.
427. Krumova EK, Bennemann P, Kindler D, et al. Low pain intensity after opioid withdrawal as a first step of a comprehensive pain rehabilitation program predicts long-term nonuse of opioids in chronic noncancer pain. Clin J Pain 2013;29(9):760–9
428. Kuhlman JJ Jr., et al. Fentanyl use, misuse, and abuse: a summary of 23 postmortem cases, Journal of Analytical Toxicology, Vol. 27, 499-504, Oct 2003.
429. Kuo JH, et al. Use and Misuse of Opioids after Endocrine Surgery Operations. *Annals of Surgery*. 2020:1-6.
430. Kurita GP, et al. Tapering off long-term opioid therapy in chronic non-cancer pain patients: a randomized clinical trial, Eur J Pain. 2018 May 13. doi: 10.1002/ejp.1241.
431. Labzda v Purdue Pharma et al, No. 01-8726-CIV-FERGUSONSNOW, 2003 WL 26100920 (S.D. Fla. 2003)
432. Lange, B., Efficacy and Safety of Tapentadol Prolonged Release for Chronic Osteoarthritis Pain and Low Back Pain, Adv Ther 27:381 (2010)
433. Langemark, M. et al. Drug Abuse in Migraine Patients, Pain, 19 (1984) 81-86
434. Lankenau SE, et al. Initiation into prescription opioid misuse amongst young injection drug users. J Drug Policy. 2012; 23(1):37–44.
435. Larach, Daniel B., et al. Patient Factors Associated with Opioid Consumption in the Month Following Major Surgery. Annals of surgery (2019).
436. Lee C, Kjaer K, Barrett J, Opioid Patient Safety Tool Kit. Weill Cornell Medicine (2019)
437. Lee M, et al. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011; 14(2):145–161.
438. Lee, J. S., et al. New persistent opioid use among patients with cancer after curative-intent surgery. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 35.36 (2017): 4042-4049.

*Lembke Report**Confidential — Subject to Protective Order*

439. Lee, Jay S., et al. Postoperative opioid prescribing and the pain scores on hospital consumer assessment of healthcare providers and systems survey. *Jama* 317.19 (2017): 2013-2015.
440. Lembke A, Chen JH. Use of opioid agonist therapy for Medicare patients in 2013. *JAMA Psychiatry*. 2016; 73(9). doi:10.1001/jamapsychiatry.2016.1390
441. Lembke A, et al. Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period. *Pain Med*. 2018;(February):1-4. doi:10.1093/pmj/pny019
442. Lembke A, et al. The Opioid Epidemic as a Watershed Moment for Physician Training in Addiction Medicine. *Acad Psychiatry*. 2018;42(2):269-272. doi:10.1007/s40596-018-0892-8.
443. Lembke A, et al. Weighing the risks and benefits of chronic opioid therapy. *Am Fam Physician*. 2016; in press.
444. Lembke A. Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop. 1st ed. Johns Hopkins University Press; 2016
445. Lembke A. Psychology of Addiction and Recovery. Lecture: History of Addiction (Stanford University, Fall/Winter 2020).
446. Lembke A., Tapering Long-Term Opioid Therapy. *Am Fam Physician* 2020; 101(1):49-52.
447. Lembke, "BRAVO! A Collaborative Approach to Opioid Tapering.", Oregon Pain Guidance, March 2020, <https://www.oregonpainguidance.org/wp-content/uploads/2020/03/BRAVO-FINAL-3.13.20-1.pdf>
448. Lembke, A. Tapering Patients off Chronic Opioid Therapy. CME course. VA BoM.
449. Lembke, A. The Opioid Epidemic: Where We Are Today (2018)
450. Lembke, A. Why Doctors prescribe opioids to known opioid abusers, *N Engl J Med* 367(17): 1580-81
451. Lembke, A., Papac, J., Humphreys, K. Our Other Prescription Drug Problem, *N Engl J Med* 2018; 378(8):693-695;
452. Lembke, Anna. BRAVOI A Collaborative Approach to Opioid Tapering. Oregon Pain Guidance March 2020 <https://www.oregonpainguidance.org/wp-content/uploads/2020/03/BRAVO-FINAL-3.13.20-1.pdf>

*Lembke Report**Confidential — Subject to Protective Order*

453. Lester, W., et al. Symptomology Associated with In Utero Exposures to Polysubstance in an Appalachian Population. Marshall Journal Of Medicine. 2019; 5(2):38-51, at pp.38,41.
454. Lets Talk Pain, Resources for Pain Management: Understanding Tolerance, Physical Dependence and Addiction. (2011) http://www.letstalkpain.org/real_story/addictions.html
455. Letter from Rogelio Guevara, Chief Inspector, DEA, to Marcia Crosse/GAO, 11/5/03; reprinted at GAO Report
456. Leung PTM, *et al.* A 1980 Letter on the Risk of Opioid Addiction. *N Engl J Med.* 2017; 376:2194-2195, at p. 2194
457. Leung PTM, Macdonald EM, Stanbrook MC, et al. Supplement to "A 1980 letter on the risk of opioid addiction." *N Engl J Med.* 2017. 376:2194-2195.
458. Lexchin J. Sponsorship bias in clinical research. *International Journal of Risk & Safety in Medicine* 2012: 233-242.
459. Li V, Pain and addiction: screening patients at risk, *Pain Med* 2001; 2(3):244, A216.
460. Liu D, et al. Implications of Chronic Opioid Therapy on Perioperative Complications and Long-Term Surgical Recovery. *Transl Perioper & Pain Med* (2019)
461. Lofwall MR, et al. Buprenorphine diversion and misuse in outpatient practice. *J Addict Med.* 2014; 8(5):327–332.
462. Loren, Alison. Harder to treat than Leukemia – Opioid use disorder in survivors of cancer. *N Engl J Med* 379;26 (2485-87) December 27, 2018
463. Lucas C, et al. Kindness Kills: the negative impact of pain as the fifth vital sign. *Journal of the American College of Surgeons*, Volume 205, Issue 1, 101 - 107 (2007)
464. Lurie J. Doctors Receive Opioid Training. Big Pharma Funds It. What Could Go Wrong? Mother Jones. <https://www.motherjones.com/politics/2018/04/doctors- are-required-to-receive-opioid-training-big-pharma-funds-it-what-could-go- wrong/>.
465. Lusher J, Analgesic addiction and pseudoaddiction in painful chronic illness. *Clin J Pain* 2006; 22(3):316-324.
466. Lynch FL, et al. Costs of care for persons with opioid dependence in commercial integrated health systems. *Addict Sci Clin Pract.* 2014;9(1):16.

*Lembke Report**Confidential — Subject to Protective Order*

467. MA Gov. Year over year opioid-related overdose deaths decline in Massachusetts; opioid prescriptions fall 30 percent, Mass.gov. Press Release. <https://www.mass.gov/news/year-over-year-opioid-related-overdose-deaths- decline-in-massachusetts-opioid-prescriptions>
468. Mack KA, et al. Physician Dispensing of Oxycodone and Other Commonly Used Opioids, 2000-2015, United States. *Pain Med.* 2018 May 1; 19(5):990-996. doi: 10.1093/pnm/pnx007.PMID: 28340060
469. MacLean RR, et al. Systemic Review of Pain Severity and Opioid Craving in Chronic Pain and Opioid Use Disorder. *Pain Medicine* (2019)
470. Malick-Searle, Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. *Journal of Multidisciplinary Healthcare* 2016;9 :447–454.
471. Manchikanti L, et al. Challenges and concerns of persistent opioid use in cancer patients. *Expert Rev Anticancer Ther.* 2018 Jul; 18(7):705-718. doi:10.1080/14737140.2018.1474103. Epub 2018 May 14.
472. Manchikanti L, et al. Controlled substance abuse and illicit drug use in chronic pain patients: an evaluation of multiple variables. *Pain Physician* 2006;9: 215–26
473. Manchikanti L, et al. Does adherence monitoring reduce controlled substance abuse in chronic pain patients? *Pain Physician* 2006;9:57–60.
474. Manchikanti L, et al. Evaluation of abuse of prescription and illicit drugs in chronic pain patients receiving short-acting (hydrocodone) or long-acting (methadone) opioids. *Pain Physician* 2005; 8:257–61.
475. Manchikanti L, et al. Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. *J Ky Med Assoc* 2003; 101:511– 17.
476. Manchikanti L, et al. Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain Physician*. 2017 Feb; 20(2S):S3-S92.
477. Manchikanti L, et al. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician*. 2008; 11:S63–S88.
478. Manchikanti L. Does random urine drug testing reduces illicit drug use in chronic pain patients receiving opioids, *Pain Physician* 2006 9(2):123-9.
479. Manchikanti L. National drug control policy and prescription drug abuse: facts and fallacies. *Pain Physician*. 2007; 10(3):399–424.

480. Manchikanti L., et al. Reframing the prevention strategies of the opioid crisis: Focusing on prescription opioids, fentanyl, and heroin epidemic. *Pain Physician* 2018; 21:309-326.
481. Manchikanti, L. et al. Prevalence of illicit drug use among individuals with chronic pain in the Commonwealth of Kentucky: an evaluation of patterns and trends. *J Kentucky Med Association* 2005; 103(2):55-62.
482. Manchikanti, L., et al. Prevalence of Opioid Abuse in Interventional Pain Medicine Practice Settings: A Randomized Clinical Evaluation. *Pain Physician*, Volume 4, Number 4, pp 358-365. 2001, American Society of Interventional Pain Physicians
483. Manchikanti, L., et al. Reframing the Prevention Strategies of the Opioid Crisis: Focusing on Prescription Opioids, Fentanyl, and Heroin Epidemic, *Pain Physician*, 2018; 21; 309-326
484. Marcus, Daniel P., et al. Prescription opioid use among opioid-naive women undergoing immediate breast reconstruction. *Plastic and reconstructive surgery* 140.6 (2017): 1081-1090.
485. Mark J, et al. Ultrarestrictive Opioid Prescription Protocol for Pain Management After Gynecologic and Abdominal Surgery. *JAMA Netw Open*. 2018; 1(8):e185452.
doi:10.1001/jamanetworkopen.2018.5452
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2717556>
486. Mark TL, Parish W, Opioid Medication Discontinuation and Risk of Adverse Opioid-Related Health Care Events. *Journal of Substance Abuse Treatment* 103 (2019) 58–63
487. Markenson JA, Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *Clinical Journal of Pain* 2005; 21 (6): 524-35.
488. Mars SG, *et al.*, “Every ‘Never’ I Said Came True”: Transitions from Opioid Pills to Heroin Injecting. *Int'l J. of Drug Policy*. 2014;25:257-266, at p. 264
489. Martell BA, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med*. 2007; 146(2):116–127.
490. Maruta, T. et al. Drug Abuse and Dependency in Patients with Chronic Pain, *Mayo Clin. Proc* 54:241-44, 1979
491. Massatti, R. Treatment Options for Opioid Use Disorder in Ohio, *Ohio Mental Health & Addiction Services*. September 28th, 2018

*Lembke Report**Confidential — Subject to Protective Order*

492. Mathis SM, et al. Provider-Patient Communication about Prescription Drug Abuse: a qualitative analysis of the perspective of prescribers. *Substance Abuse* (2019)
493. Matsumoto A. Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: results of a randomized, double-blind, placebo- and active-controlled phase III trial, *Pain Medicine* 2005;6(5):357-366.
494. Matthias MS, et al. 'I Was a Little Surprised': Qualitative Insights From Patients Enrolled in a 12-Month Trial Comparing Opioids With Nonopioid Medications for Chronic Musculoskeletal Pain. *J Pain*. 2018 Apr 30. pii:S1526- 5900(18)30158-5. doi:10.1016/j.jpain.2018.04.008.
495. McAnally HB. Chapter 10: Opioid Dependence Risk Factors and Risk Assessment. *Opioid Dependence* (Book, 2018)
496. McCabe SE, et al. A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife. *Drug Alcohol Depend*. 2019. doi:10.1016/j.drugalcdep.2018.10.027
497. McCabe SE, et al. Medical and nonmedical use of prescription opioids among high school seniors in the United States. *Arch Pediatr Adolesc Med*. 2012. doi:10.1001/archpediatrics.2012.85
498. McCabe, Sean Esteban, et al. Trends in medical and nonmedical use of prescription opioids among US adolescents: 1976–2015. *Pediatrics* 139.4 (2017): e20162387.
499. McCance-Katz NSDUH Report 2018
500. McCarthy M. Illicit drug use in the US holds steady, but heroin use is on rise. *BMJ*. 2013; 347(September):f5544.
501. McCaskill Senate Homeland Security & Governmental Affairs Committee. Fueling an Epidemic, Report 2: Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups at p. 1, p. 4 and p. 17
502. McCaskill, Claire, BREAKING: Millions in Payments Among Findings of McCaskill Opioid Investigation into Ties Between Manufacturers and Third Party Advocacy Groups, Press Release 2018
503. McDonald DC, et al. Estimating the prevalence of opioid diversion by 'doctor shoppers' in the United States. *PLoS One*. 2013;8(7):e69241. doi:10.1371/journal.pone.0069241.
504. McDonald DC, et al. Geographic variation in opioid prescribing in the U.S. *J Pain*. 2012;13(10):988–996.

*Lembke Report**Confidential — Subject to Protective Order*

505. McIlwain H, Safety, tolerability, and effectiveness of oxymorphone extended release for moderate to severe osteoarthritis pain. A one year study. American Journal of Therapeutics 2005; 12, 106-112.
506. McKnight v Purdue Pharma et al., No. 9:04 Civ-116, 2005 WL 5794391 (E.D.Texas 2005)
507. McLellan AT, et al. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. JAMA. 2000; 284:1689–1695.
508. McNicol, et al. Opioids for neuropathic pain, Cochrane Database Syst Rev. 2013 Aug 29; (8):CD006146.
509. MDL 2804, Opinion and Order Granting in Part Defendant's Motion to Exclude Marketing Causation Opinions of Schumacher, Lembke and Keyes (2019.08.27 Dkt no. 2549)
510. MDL 2804, Order re Defendant's Motion to Exclude Expert Testimony of Katherine Keyes, Anna Lembke and Jonathan Gruber re the Gateway Hypothesis of Causation (2019.08.26 Dkt no. 2518)
511. Medina, J, et al. Drug Dependency in Patients with Chronic Headaches. Headache 17: 12-14, 1977.
512. Meier B. Pain Killer: A Wonder Drug's Trail of Addiction and Death. St. Martin's Press; 2003
513. Meisel, Zachary F., et al. Conversion to Persistent or High-Risk Opioid Use After a New Prescription From the Emergency Department: Evidence From Washington Medicaid Beneficiaries. Annals of emergency medicine (2019).
514. Meldrum ML, A capsule history of pain management. JAMA. 2003; 290(18):2470–2475.
515. Meldrum ML. Opioids and Pain Relief: A Historical Perspective (Progress in Pain Research and Management, V. 25). IASP Press; 2003, at pp. 195-199
516. Meltzer EC, et al. Aberrant drug-related behaviors: Unsystematic documentation does not identify prescription drug use disorder. Pain Med 2012;13:1436–43
517. Meltzer EC, et al. Identifying prescription opioid use disorder in primary care: diagnostic characteristics of the Current Opioid Misuse Measure (COMM). Pain 2011; 152:397–402.

518. Meske, et al. Efficacy of opioids versus placebo in chronic pain: a systematic review and meta-analysis of enriched enrollment randomized withdrawal trials, *J Pain Res.* 2018 May 3; 11:923-934.
519. Michna EJ, Urine toxicology screening among chronic pain patients on opioid therapy: frequency and predictability of abnormal findings, *Clin J Pain* 2007; 23(2):173-9.
520. Mikosz, C. et al. Indication-Specific Opioid Prescribing for US Patients With Medicaid or Private Insurance, 2017. *JAMA Network Open.* 2020;3(5):e204514
521. Miller M, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Intern Med.* 2015 Apr; 175(4):608-15. doi: 10.1001/jamainternmed.2014.8071.
522. Miller NS, Swiney T, Barkin RL. Effects of opioid prescription medication dependence and detoxification on pain perceptions and self-reports. *Am J Ther* 2006;13(5):436-44.
523. Milligan K, et al. Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. *J Pain* 2001; 2:197–204
524. Minozzi, Silvia, Laura Amato, and Marina Davoli. "Development of dependence following treatment with opioid analgesics for pain relief: a systematic review." *Addiction* 108.4 (2013): 688-698.
525. Mironer YE, et al. Relative misuse potential of different opioids: A large pain clinic experience. Atlanta, GA: American Pain Society; 2000
526. Mitchell, Jerry, How the FDA helped pave way for opioid epidemic, *Clarion Ledger*, 2018
527. Mojtabai R., et al. National trends in long-term use of prescription opioids. *Pharmacoepidemiol Drug Saf.* 2018 May; 27(5):526-534. doi: 10.1002/pds.4278. Epub 2017 Sep 6.
528. Moore, et al., Benefits and harms associated with analgesic medications used in the management of acute dental pain. 2018; 149: 256-263, *J Am Dental Assoc.* 2018; 149: 256-265.
529. Morasco BJ, Dobscha SK. Prescription medication misuse and substance use disorder in VA primary care patients with chronic pain. *Gen Hosp Psychiatry* 2008; 30:93–9.
530. Moulin DE, et al. Randomised trial of oral morphine for chronic non-cancer pain. *Lancet* 1996; 347:143–7

*Lembke Report**Confidential — Subject to Protective Order*

531. Muhuri PK, et al. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. CBHSQ Data Review, 2013
532. Mullican WS, Tramadol/acetaminophen combination tablets and codeine/acetaminophen combination capsules for the management of chronic pain: A comparative trial, Clinical Therapeutics 2001; 23 (9).
533. Multiple Chronic Conditions Resource Center. Chronic Pain Guidelines.
534. Muriel J, et. al., Pharmacogenetics and Prediction of Adverse Events in Prescription Opioid Use Disorder Patients. Basic Clin Pharmacol Toxicol. 2019;124:439–448
535. Murphy JL, Clark ME, Banou E. Opioid cessation and multidimensional outcomes after interdisciplinary chronic pain treatment. Clin J Pain 2013;29 (2):109–17.
536. Murphy JL, Phillips KM, Rafie S. Sex differences between veterans participating in interdisciplinary chronic pain rehabilitation. J Rehabil Res Dev 2016; 53(1):83–94
537. Mystakidou D, Long-term management of noncancer pain with transdermal therapeutic system-fentanyl. The Journal of Pain 2003 4, (6):298-306
538. Naliboff BD, et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. J Pain 2011;12:288–96
539. National Academies of Science Engineering and Medicine (NASEM). Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use; 2017. doi:10.17226/24781, at p.51 (emphasis added).
540. National Academies of Sciences, Engineering, and Medicine (NASEM 2020). 2020. *Framing Opioid Prescribing Guidelines for Acute Pain: Developing the Evidence*. Washington, DC: The National Academies Press..<https://www.nap.edu/catalog/25555/framing-opioid-prescribing-guidelines-for-acute-pain-developing-the-evidence>
541. Nestler EJ. Is there a common molecular pathway for addiction?, Nat Neurosci. 2005;8(11):1445–1449.
542. Nicolas MK. Using opioids with persisting noncancer pain; a biopsychosocial perspective. Clin J Pain 2006;22(2):137-46.
543. Nilsen HK, Stiles TC, Landro NI, et al. Patients with problematic opioid use can be weaned from codeine without pain escalation. Acta Anaesthesiol Scand 2010;54(5):571–9.

*Lembke Report**Confidential — Subject to Protective Order*

544. Noble M., et al. Long-term opioid management for chronic noncancer pain (Review). The Cochrane Collaboration. April 8, 2008.
545. Noble, M., et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010(1):CD006605.
546. Nurnberger J. Evidence for a locus on chromosome 1 that influences vulnerability to alcoholism and affective disorder, *Am J Psychiatry* 2001;158:718-724.
547. O'Brien Aff. Branch v. Purdue Pharma L.P., No. LR 1696-3, WL 3752789. (D. Tex filed January 20, 2004).
548. O'Brien Aff. Campbell v. Purdue Pharma L.P., No. 1:02CV00163TCM, WL 6057307. (E.D. Mo., filed January 14, 2004).
549. O'Brien Aff. Harris v. Purdue Pharma L.P., No. C-1-01-428, WL 4012102. (S.D. Ohio, filed August 18, 2004).
550. O'Brien Aff. Labzda v. Purdue Pharma L.P., No. 01-8726-CIV-FERGUSON/SNOW, WL 26100920. (S.D. Fla., filed March 31, 2003).
551. O'Brien Aff. McKnight v. Purdue Pharma Company, No. 9:04 Civ.-116, WL 5794391. (E.D. Tex., filed June 6, 2005).
552. O'Brien Aff. Savant v. Purdue Pharma Company, No. 04-394-DRH, WL 6503987. (S.D. Ill., filed December 7, 2005).
553. O'Brien Aff. Taylor v. Purdue Pharma Company, No. 504-CV-197, WL 3578006. (M.D. Ga., filed June 7, 2005).
554. O'Brien, Charles. "Addiction and dependence in DSM-V." *Addiction* 106.5 (2011): 866-867.
555. Oei JL, et al. Neonatal Abstinence Syndrome and High School Performance. *Pediatrics*. 2017;139(2):e20162651, at p. 7
556. Oei, Ju Lee, et al. "Neonatal abstinence syndrome and high school performance." *Pediatrics* 139.2 (2017): e20162651.
557. Office of Epidemiology and Prevention Services Outbreak Report Opioid-Related Overdose — Huntington, West Virginia, August 2016

*Lembke Report**Confidential — Subject to Protective Order*

558. Office of Inspector General Review of the Drug Enforcement Administration's Regulatory and Enforcement Efforts to Control the Diversion of Opioids (2019) <https://oig.justice.gov/reports/2019/a1905.pdf>.
559. Office of the National Coordinator for Health Information Technology. "What is Clinical Decision Support (CDS)?" April 10, 2018. At <https://www.healthit.gov/topic/safety/clinical-decision-support>.
560. OH Laws File, H.B. No. 187 - Health Care providers - Physicians - Treatment and Intractable Pain, 1997 Ohio Laws File 46 (H.B. 187)
561. OH Legislative Service Commission, Ohio Final Bill Analysis, 1997 House Bill 187, OH B. An. 1997 H.B. 187
562. OH Revised Code Annotated, 2925.02 Corrupting another with drugs, OH ST § 2925.02, OH ST § 2925.02
563. OH Revised Code Annotated, 3719.011 Definitions of controlled substance, drug dependence, OH ST § 3719.011, OH ST § 3719.011
564. OH Revised Code Annotated, OH ST § 4731.052 - Diagnosis and management of chronic pain; use of controlled substances or products containing tramadol, OH Revised Code Annotated
565. Ohio Admin. Code §4731-21
566. Ohio House of Representative. Prescription Drug Addiction and Healthcare Reform Legislative Study Committee. Chairman's Report. October 17, 2013.
567. Okie, S. A flood of opioids a rising tide of deaths. N. Engl. J. Med. 363;21. 1981- 85.
568. Olsen, M.F., et al. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. BMC Medicine (2017) 15:35 DOI 10.1186/s12916-016-0775-3
569. Olsson MO, et al. High rates of tramadol use among treatment-seeking adolescents in Malmo, Sweden: a study of hair analysis of nonmedical prescription opioid use. *Journal of Addiction* 2015:1-9, at p. 1.
570. Olsson MO, Öjehagen A, Brådvik L, Kronstrand R, Håkansson A. High Rates of Tramadol Use among Treatment-Seeking Adolescents in Malmö, Sweden: A Study of Hair Analysis of Nonmedical Prescription Opioid Use. *Journal of addiction*. 2017; 2017:6716929. [pubmed]

*Lembke Report**Confidential — Subject to Protective Order*

571. Opioids for Acute Pain: Get the Facts, Ctrs. for Disease Control and Prevention. <https://www.cdc.gov/drugoverdose/pdf/patients/Get-the-Facts-a.pdf>
572. Oregon Health Authority Oregon Opioid Taper Guidelines Task Force Resources. See <https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/SUBSTANCEUSE/OPIOIDS/Documents/taskforce/tapering-taskforce/2019-Opioid-Taper-Task-Force-Resources.pdf>.
573. Orhurhu V et al. Trends of opioid use disorder among hospitalized patients with chronic pain. *Pain Practice*. 2019;19(6): 656-663, at p. 656.
574. Orliaguet G, Hamza J, Couloigner V, et al. A case of respiratory depression in a child with ultrarapid CYP2D6 metabolism after tramadol. *Pediatrics*. 2015; 135(3):e753-5. [pubmed]
575. Ornstein C, et al. American Pain Foundation shuts down as senators launch an investigation of prescription narcotics. ProPublica, May 8, 2012. <https://www.propublica.org/article/senate-panel-investigates-drug-company-ties-to-pain-groups>. Accessed March 20, 2016
576. Osmundson SS, et al., Opioid prescribing after childbirth and risk for serious opioid-related events: a cohort study. *Annals of Internal Medicine* 2020; doi:107326/M19-3805, at p. 2.
577. Pain Medicine Editors' page. Official Journal of the AAPM. *Pain Medicine*. V.9(4) (2008)
578. Palangio M, A. Combination Hydrocodone and ibuprofen versus combination codeine and acetaminophen for the treatment of chronic pain. *Clinical Therapeutics* 2000; 22 No 7.
579. Park-Lee E, et al. Receipt of Services for Substance Use and Mental Health Issues Among Adults: Results from the 2016 National Survey on Drug Use and Health. Source CBHSQ Data Review. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2012-2017 Sep.
580. Parloff R. Tapering off long-term Rx opioids: a first-hand account, Opioid Institute. (October 15, 2018) See <https://opioidinstitute.org/2018/10/15/tapering- opioids-lembke/>.
581. Parr G. Joint pain and quality of life; results of a randomized trial. *Br J Clin Pharmac* 1989; 27:235-242.
582. Passik S, Pain clinicians' rankings of aberrant drug-taking behaviors, *J Pain & Palliative Care* 2002; 16(4): 39-49.

*Lembke Report**Confidential — Subject to Protective Order*

583. Passik SD, et al. Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. *J Pain Symptom Manage* 2011; 41:116–25.
584. Passik SD, et al. Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the pain assessment and documentation tool. *J Opioid Manage* 2005; 1:5
585. Passik SD, et al. Pseudoaddiction revisited: a commentary on clinical and historical considerations. *Pain Manag*. 2011 May;1(3):239-48.
doi:10.2217/pmt.11.12.PMID:24646390
586. Passik, SD, et al. Prevalence of substance abuse disorders in cancer patients, *Oncology* 12(4): 517-521, 1998
587. Patrick Morrisey "DEA's Failure to Combat Diversion Cost Lives: Results from the West Virginia Attorney General's Investigation into the DEA's Catastrophic Failure to Manage the National Drug Quota System from 2010-2016" West Virginia Office of the Attorney General June 4 2020
588. Paulozzi LJ, et al. A national epidemic of unintentional prescription opioid overdose deaths: how physicians can help control it. *J Clin Psychiatry*. 2011;72(5):589-592.
doi:10.4088/JCP.10com06560
589. Paulozzi LJ, et al. Vital signs: overdoses of prescription opioid pain relievers— United States, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2011; 60(43):1487– 1492.
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm?s_cid=mm6043a4_w.
590. Paulozzi LJ, et. al. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiology and Drug Safety*. 2006;15:618-627, at p. 621.
591. Paulozzi, LJ. MD, et al. US data show sharply rising drug-induced death rates, *Injury Prevention* 2007;13:130–132. doi: 10.1136/ip.2006.014357
592. Paulozzi, LJ. MD. Prescription drug overdoses: A Review of Safety Research 43(2012) 283-89
593. Peacock, Amy, et al. Opioid use and harms associated with a sustained-release tapentadol formulation: A post-marketing surveillance study. *Drug and Alcohol Dependence* (2019): 107697.
594. Peloso PM. Double Blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee, *The Journal of Rheumatology* 2000; 27:3.

*Lembke Report**Confidential — Subject to Protective Order*

595. Perez-Mana C, et al. Drug Interactions with New Synthetic Opioids. *Front. Pharmacol.* (2018)
596. Pergolizzi, Joseph V., et al. Tapentadol extended release in the treatment of severe chronic low back pain and osteoarthritis pain. *Pain and therapy* 7.1 (2018): 37-57.
597. Perry, S., et al. Management of Pain during Debridement: a Survey of U.S. Burn Units. *Pain*, 13 (1982) 267-280.
598. Pestka E, Evans M. Family History of Substance Use Disorder and Chronic Pain Management. *Nurse Practitioner* (2018)
599. Peter Whoriskey "How Johnson & Johnson companies used a 'super poppy' to make narcotics for America's most abused opioid pills" Washington Post, March 26, 2020 <https://www.washingtonpost.com/graphics/2020/business/opioid-crisis-johnson-and-johnson-tasmania-poppy/>
600. Peters, *et.al.*, "HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014-2015" *N Engl J Med* 2016;375:229-39, at pp. 229 and 232.
601. Pielech, *et al.*, Receipt of Multiple Outpatient Prescriptions Is Associated With Increased Risk of Adverse Outcomes in Youth: Opioid Prescribing Trends, Individual Characteristics, and Outcomes from 2005-2016. *PAIN* 2020, published ahead of print. DOI:10.1097/j.pain.0000000000001812, at p. 2 (emphasis in original).
602. Pitcher MH, Von Korff M, Bushnell MC, Porter L. Prevalence and Profile of High-Impact Chronic Pain in the United States. *J Pain*. 2019;20(2):146-160. doi:10.1016/j.jpain.2018.07.006.
603. Pitt, Allison, et al. Modeling Health Benefits and Harms of Public Policy Responses to the US Opioid Epidemic. *Am J Public Health*. 2018; 108:1394– 1400. doi:10.2105/AJPH.2018.304590
604. Polak, Anne "The Addiction Recovery Medical Home As An Alternative Payment Model," *Health Affairs Blog*, December 12, 2018. DOI: 10.1377/hblog20181211.111071. *Heal Aff Blog*. doi: 10.1377/hblog20181211.111071, at p. 3.
605. Portenoy RK, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain* 2007; 23:287-99.
606. Portenoy RK. Chronic opioid therapy in nonmalignant pain. *J Pain Symptom Manage* 1990; 5:46–62

*Lembke Report**Confidential — Subject to Protective Order*

607. Portenoy RK. Chronic use of opioid analgesics in non-malignant pain: Report of 38 cases, Pain 1986; 25: 171-186.
608. Portenoy, RK. Chronic opioid therapy for nonmalignant pain: from models to practice. APS Journal 1992; 1:285-288.
609. Portenoy, RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage 1996; 11(4):203-217.
610. Porter J, et al. Addiction rare in patients treated with narcotics. N Engl J Med. 1980;302(2):123.
611. Prescrire. "Weak" opioid analgesics. Codeine, dihydrocodeine and tramadol: no less riskt than morphine. Translate from Rev Prescrire Nov 2015; 35 (385): 831-38
612. Prescrire. Paracetamol + Tramadol. Prescrire Int. Dec. 2003 vol. 12 (68) 211-13
613. President's Council of Economic Advisors' (CEA) The Role of Opioid Prices in the Evolving Opioid Crisis 2019 Report, <https://www.whitehouse.gov/wp-content/uploads/2019/04/The-Role-of-Opioid-Prices-in-the-Evolving-Opioid-Crisis.pdf>,
614. Press Release, Actavis, Actavis Acquires Kadian; Extends Specialty Drug Portfolio in U.S., (Dec. 30, 2008),
<https://www.businesswire.com/news/home/20081230005227/en/Actavis-Acquires-Kadian-Extends-Specialty-Drug-Portfolio>.
615. Press Release: One-Third of Americans Have Received an Opioid Prescription in the Past Two Years, NORC at the University of Chicago, September 27, 2018.
<https://www.norc.org/NewsEventsPublications/PressReleases/Pages/one-third-of-americans-have-received-an-opioid-prescription-in-the-past-two-years.aspx>
616. Private ARCOS data produced by defendants, as evaluated by Craig McCann
617. Purdue Pharma Butrans Product Alert, September 2011,
http://rphmail.com/ch/2011/butrans_101411.html
618. Purdue Pharma L.P. Letter from Stephen L. Seid to Healthcare Professionals re Butrans, dated September 2011.
619. Quang-Cantagrel N D, et al. Opioid substitution to improve the effectiveness of chronic noncancer pain control: A chart Review. Anesth Analg 2000; 90:933–7

*Lembke Report**Confidential — Subject to Protective Order*

620. Raber I, Ball A, et al. Qualitative Assessment of Clerkship Students' Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum. *Acad Psychiatry*. 2018;42(5):664-667.
621. Radel, Laura, et al. Substance use, the opioid epidemic, and the child welfare system: Key findings from a mixed methods study. Office of the Assistant Secretary for Planning and Evaluation (2018).
622. Raheemullah, A., Lembke, A. Buprenorphine Induction Without Opioid Withdrawal: A Case Series of 15 Opioid-Dependent Inpatients Induced on Buprenorphine Using Microdoses of Transdermal Buprenorphine. *American Journal of Therapeutics*, 2019; 0:1-7.
623. Raheemullah, A., Lembke, A. Initiating Opioid Agonist Treatment for Opioid Use Disorder in the Inpatient Setting: A Teachable Moment, *JAMA Internal Medicine*, 2019; 179(3):427-428.
624. Raja SN. Opioids versus antidepressants in postherpetic neuralgia. A randomized, placebo-controlled trial, *Neurology* 2002; 59.
625. Raja, S. et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *PAIN* 00 (2020) 1–7
626. Rangel-Guerra R. An open evaluation of oral butorphanol as long-term therapy in outpatients suffering from moderate to severe chronic pain, *J Int Med Res* 1981;9:120-123.
627. Rayport, M., et al. Experience in the Management of Patients Medically Addicted to Narcotics. *JAMA* vol. 156 (7), 684-691. Oct. 16, 1954
628. Reid MC, et al. Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med* 2002; 17:173–9.
629. Rhodin A. Methadone treatment of chronic non-malignant pain and opioid dependence—a long-term follow-up, *European J Pain* 2006; 10(3):271-8.
630. Rich, Ben A. Physicians' legal duty to relieve suffering, *West J Med*. 2001 Sep; 175(3): 151–152.
631. Rieder TN. In opioid withdrawal, with no help in sight. *Health Aff*. 2017; 36(1):182-185. doi:10.1377/HLTHAFF.2016.0347
632. Ries RK, et al. The ASAM Principles of Addiction Medicine. 5th ed. Philadelphia: Lippincot Williams and Wilkins; 2014.

*Lembke Report**Confidential — Subject to Protective Order*

633. Robbbins, L, MD. Oxycodone CE, a Long-acting Opioid, for Severe Chronic Daily Headache. *Headache Q* 1999; 19:305-309.
634. Robert Crow Linkedin Profile, <https://www.linkedin.com/in/robert-crow-7b97aa192>
635. Robert Wood Johnson Foundation Financial Statements Dec. 31, 2017 and 2016 (With Independent Auditors' Report Thereon), <https://www.rwjf.org/content/dam/files/rwjf-web-files/Financials/FY2017-RobertWoodJohnsonFdn-FS.pdf>
636. Roberts, Karl C., et al. "Prescribing and Consumption of Opioids After Primary, Unilateral Total Hip and Knee Arthroplasty in Opioid-Naive Patients." *The Journal of Arthroplasty* (2019).
637. Robins LN, et al. How permanent was Vietnam drug addiction? , *Am J Public Health*. 1974; 64(12 Sup):38-43. doi:10.2105/AJPH.64.12_Suppl.38
638. Robinson M, Wittmer V, George S, Beneciuk J, Fillingim R. Opiates for chronic pain: To wean or not to wean. *J Pain* 2008;9(4):51
639. Roddy J, Steinmiller CL, Greenwald MK. Heroin purchasing is income and price sensitive. *Psychol Addict Behav*. 2011;25(2):358-364. doi:10.1037/a0022631
640. Rogers AH, et al. The Interaction of Alcohol Use and Cannabis Use Problems in Relation to Opioid Misuse Among Adults in Chronic Pain. *International Journal of Behavioral Medicine* (2019)
641. Rollnick S, Miller W. What is Motivational Interviewing? *Behavioural and Cognitive Psychotherapy*. 1995;23(4):325-334.
642. Rome JD, Townsend CO, Bruce BK, et al. Chronic noncancer pain rehabilitation with opioid withdrawal: Comparison of treatment outcomes based on opioid use status at admission. *Mayo Clin Proc* 2004; 79(6):759–68
643. Romman AN, et al. Opioid Prescribing to Medicare Part D Enrollees, 2013-2017: shifting responsibility to pain management providers. *Pain Medicine*. 2020; 0(0): 1-9.
644. Rose SL, et al., Patient Advocacy Organizations, Industry Funding and Conflicts of Interest. *JAMA Intern Med*. (2017): 177(3):344-350
645. Rosenberg JM, et al. Opioid Therapy for Chronic Pain: overview of the 2017 US Department of Veterans Affairs and US Department of Defense clinical practice guidelines. *Pain Medicine*. 2018;19:928-941, at p. 930

*Lembke Report**Confidential — Subject to Protective Order*

646. Rosner B, Neicun J, Yan JC, Roman-Urrestarazu A. Opioid Prescription Patterns in Germany and the Global Opioid Epidemic: systemic review of available evidence. *Plos One* (2019)
647. Roth SH. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain. *Arch Intern Med* 2000; 160:853-860.
648. Rowbotham MC. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Eng J Med* 2003;348(13):1223-32.
649. Rubin, R. Limits on Opioid Prescribing Leave Patients With Chronic Pain Vulnerable. *JAMA*. 2019. E1-E3
650. Rudd RA, et al. Increases in drug and opioid overdose deaths—United States, 2000–2014. *MMWR Morb Mortal Wkly Rep*. 2016; 64:1378–1382.
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm>
651. Ruhm CJ. Deaths of Despair or Drug Problems? NBER Working Paper No. 24188, NBER Program(s):Health Care, Health Economics, Public Economics (2017).
652. Ruhm CJ. Drug involvement in fatal overdoses. *SSM - Popul Heal*. 2017. doi:10.1016/j.ssmph.2017.01.009
653. Ruhm, C. Understanding the Fatal Drug Epidemic. University of Virginia. CSAM. August 31, 2018.
654. Ruhm, CJ. Geographic Variation in Opioid and Heroin Involved Drug Poisoning Mortality Rates. *Am J Prev Med* 2017;53(6):745–753
655. Ryan NE, Isbister GK. Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. *Clinical Toxicology* 2015;53:545-550, at p. 545.
656. Salzman RT. Long-term comparison of suprofen and propoxyphene in patients with osteoarthritis. *Pharmacology* 1983; 27 suppl. 1:55-64.
657. SAMHSA Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health
658. SAMHSA, Reports and Detailed Tables from the 2017 National Survey on Drug Use and Health (NSDUH). SAMHSA
659. Sandoe E, et al. Policy Levers That States Can Use To improve Opioid Addiction Treatment and Address the Opioid Epidemic, *Health Affairs Blog*. (Oct. 2, 2018). See <https://www.healthaffairs.org/do/10.1377/hblog20180927.51221/full/>

*Lembke Report**Confidential — Subject to Protective Order*

660. Santa Clara 6th Am. Compl. June 8, 2018 No. 30-2014-00725287
661. Santosa, Katherine B., et al. New persistent opioid use among older patients following surgery: A Medicare claims analysis. *Surgery* (2019).
662. Saper, JR. January 2, 2008 Letter from Saper to Dr. J. Paice and Dr. B.T. Sitzman re Opioid Guidelines (MDL No. 2804 Saper Dep. Ex. 3)
663. Saper, JR. January 2, 2008 Letter from Saper to Dr. Roger Chou re Opioid Guidelines (MDL No. 2804 Saper Dep. Ex. 2)
664. Saper, JR. Migraine Headache and Head Pain Treatment (MHNI), New Migraine Study, MHNI. October 23, 2017. <https://www.mhni.com/updates/new-migraine-study>. (MDL No. 2804 Saper Dep. Ex. 5)
665. Saper, JR. Curriculum vitae (MDL No. 2804 Saper Dep. Ex. 1)
666. Saper, JR. More on the Pain Debate, 3/24/2010. (MDL No. 2804 Saper Dep. Ex. 7)
667. Saper, JR. Opioid Treatment Guidelines, Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. Choe, R. et al. *The Journal of Pain*, Vol 10, No 2 (February), 2009: pp 113-130. (MDL No. 2804 Saper Dep. Ex. 4)
668. Saper, JR. The Influence of Pharma and Device manufacturers on APS and Other PMA'S. A war within a war. September 27, 2010. (MDL No. 2804 Saper Dep. Ex. 6)
669. Savant v Purdue Pharma et al., No. 04-394-DRH, 2005 WL 6503987 (S.D.Ill. 2005)
670. Schaffer-Vargas G, et al. Opioid for non-malignant pain experience of Venezuelan Center, 9th World Congress on Pain. 1999; 289:345
671. Scheck J. "Tramadol: The Opioid Crisis for the Rest of the World." *The Wall Street Journal*. Oct. 19, 2016. At <https://www.wsj.com/articles/tramadol-the-opioid-crisis-for-the-rest-of-the-world-1476887401>
672. Schedules of Controlled Substances: Placement of Tramadol into Schedule IV. 79 Fed. Reg. 37,628 (July 2, 2014).at p. 37628
673. Schieber LZ, Guy GP Jr, Seth P, et al. Supplementary Online Content to Trends and patterns of geographic variation in opioid prescribing practices by state, United States, 2006-2017. *JAMA Netw Open*. 2019;2(3):e190665.

*Lembke Report**Confidential — Subject to Protective Order*

674. Schieber, L., et al. Trends and Patterns of Geographic Variation in Opioid Prescribing Practices by State, United States, 2006-2017, JAMA Netw Open <https://www.ncbi.nlm.nih.gov/pubmed/30874783>
675. Schneider JP, et al. Defining clinical issues around tolerance, hyperalgesia, and addiction: a quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. *J Opioid Manag* 2010; 6:385–95.
676. Schnoll SH. Misconceptions and Realities of the Prescription Opioid Epidemic. *Clinical Pharmacology & Therapeutics* (2018)
677. Schofferman J. Long-term opioid analgesic therapy for severe refractory lumbar spine pain, *The Clinical Journal of Pain* 1999; 15 (2) 136-140.
678. Scholten W, Henningfield JE, Negative Outcomes of Unbalanced Opioid Policy Supported by Clinicians, Politicians and the Media. *Journal of Pain & Palliative Care Pharmacotherapy* (2019)
679. Schroeder AR, et al. Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and Abuse. *JAMA Intern Med.* 2018
680. Schubert, W. Commentary on: The Opioid Epidemic - Who is Responsible and What is the Solution? *Craniomaxillofac Trauma Reconstruction*, 2018; 11; 111- 113
681. Schuchatm Anne, et al. New Data on Opioid Use and Prescribing in the United States, *JAMA*, August 1, 2017; 318(5); 425-26.
682. Schug SA, Manopas A. Update on the role of non-opioids for postoperative pain treatment. *Best Pract Res Clin Anaesthesiol.* 2007;21(1):15-30.
doi:10.1016/j.bpa.2006.12.002
683. Schultz W. Potential vulnerabilities of neuronal reward, risk, and decision mechanisms to addictive drugs. *Neuron*. 2011; 69(4):603–617.
684. Schulzeck S. Factors contributing to the results of long-term treatment with oral morphine tablets in patients with chronic non-malignant pain, *Anaesthetist* 1993; 42: 545-556
685. Schwartz LM, Woloshin S. Medical Marketing in the United States, 1997-2016. *JAMA*. 2019; 321(1):80-96

*Lembke Report**Confidential — Subject to Protective Order*

686. Schwartz, Sherwyn, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Current medical research and opinion* 27.1 (2011): 151-162.
687. Schwarzer A, Aichinger-Hinterhofer M, Maier C, Vollert J, Walther JW. Sleep-disordered breathing decreases after opioid withdrawal: Results of a prospective controlled trial. *Pain* 2015;156 (11):2167–74
688. Securities and Exchange Commission. Teva Pharmaceutical Industries Limited Form 6-K May 2011
689. Sees K. Non-medical use of OxyContin tablets in the United States, *Pain Palliative Care Pharmacotherapy* 2005;19(2):13-23.
690. Sekhon R, et al. Compliance with opioid treatment guidelines for chronic non- cancer pain (CNCP) in primary care at a Veterans Affairs Medical Center (VAMC). *Pain Med* 2013; 14:1458–556.
691. Sekhri, Shaina, et al. Probability of opioid prescription refilling after surgery: does initial prescription dose matter?. *Annals of surgery* 268.2 (2018): 271-276.
692. Selemon, LD. A role for synaptic plasticity in the adolescent development of executive function. *Transl Psychiatry*. 2013; 3:e238. doi:10.1038/tp.2013.7
693. Senate Homeland Security and Gov Affairs Comm, 116th Cong., Report on Fueling an Epidemic Report Two: Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups (2018) at pp. 10-11,
<https://www.hsgac.senate.gov/imo/media/doc/REPORT-Fueling%20an%20Epidemic-Exposing%20the%20Financial%20Ties%20Between%20Opioid%20Manufacturers%20and%20Third%20Party%20Advocacy%20Groups.pdf>.
694. Senay EC, et al. Physician dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. *Drug and Alcohol Dependence* 2003;69:233-241, at p. 233.
695. Seth, Puja, et al. Quantifying the Epidemic of Prescription Overdose Deaths, *AJPH Surveilland*, 2018; 108(4) 500-02
696. Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* 2017;66:265–269

697. Shanahan M, Larance B, Nielsen S, Cohen M, Schaffer M, Campbell G. A Protocol for Discrete Choice Experiment: understanding patient medicine preferences for managing chronic non-cancer pain. *BMJ Open* (2019)
698. Sharp MJ, et al. Poisoning deaths involving opioid analgesics - New York State, 2003-2012. *MMWR Morb Mortal Wkly Rep.* 2015 Apr 17; 64(14):377-80. Erratum in: *MMWR Morb Mortal Wkly Rep.* 2015 Oct 16; 64(40):1154-5. PMID:25879895
699. Shauer, CKMW, et al. The fentanyl patch boil-up – A novel method of opioid abuse, *Basic & Clinical Pharmacology & Toxicology*, 2015, 117, 358–359.
700. Sherry, Tisamarie B., et al. Documented Pain Diagnoses in Adults Prescribed Opioids: Results from the National Ambulatory Medical Care Survey, 2006-2015. *Annals of Int. Med.* Sept 2018: 1-4
701. Shindo M, et al. Opioid Prescribing Practice and Needs in Thyroid and Parathyroid Surgery. *JAMA Otolaryngology - Head and Neck Surgery*. 2018
702. Simpson Jr RK. Transdermal fentanyl as treatment for chronic low back pain. *Journal of Pain and Symptom Management* 1997;
703. Singer, J. A, et al. Today's nonmedical opioid users are not yesterday's patients; implications of data indicating stable rates of nonmedical use and pain reliever use disorder. *Journal of Pain Research* 2019;12 617–620.
704. Singer, Jeffrey. Stop Calling it an Opioid Crisis—It's a Heroin and Fentanyl Crisis, Cato at Liberty, 2018
705. Sismondo S. Key Opinion Leaders and the Corruption of Medical Knowledge: what the Sunshine Act will and won't cast light on. *Journal of Law, Medicine Ethics.* 14(3): 2013
706. Skurtveit S, et al. To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use?, *Pain* 2011;152:1555–61.
707. Slavova, Svetla, et al. Methodological Complexities in Quantifying Rates of Fatal Opioid-Related Overdose. *Current Epidemiology Reports* (2019): 1-12.
708. Slomski, Anita MA, Informing Physicians of Fatal Overdose Curbs Opioid Prescribing. *JAMA*, September 25, 2018; 320(12); 1231.
709. Smith, M. et al. Nonmedical use and abuse of scheduled medications prescribed for pain, pain-related symptoms, and psychiatric disorders: patterns, user characteristics, and management options. *Current Psychiatry Reports* 2005; 7:337-343.

*Lembke Report**Confidential — Subject to Protective Order*

710. Smith, S.R., et al. Comparative pain reduction of oral non-steroidal anti- inflammatory drugs and opioids for knee osteoarthritis: Systematic analytic review. *Osteoarthritis and Cartilage* 24(6):962-972.
711. Solomon, et al. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med.* 2010 Dec 13; 170(22):1968-76.
712. Southam MA. Transdermal fentanyl therapy: system design, pharmacokinetics and efficacy. *Anticancer Drugs.* 1995;6 Suppl 3:29-34. doi:10.1097/00001813-199504003-00005
713. Spiller HA, et al. Effect of scheduling tramadol as a controlled substance on poison center exposures to tramadol. *Annals of Pharmacotherapy* 2010;44:1016-1021, at p 1017
714. Spithoff S, et al. Drivers of the opioid crisis: an appraisal of financial conflicts of interest in clinical practice guideline panels at the peak of opioid prescribing. *PLOS One.* (2020).
715. Stamer UM, et al. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. *Clinical Pharmacology & Therapeutics* 2007;82(1):41-47.
716. Stark MM, et al. People can die from opiate withdrawal. *Med Sci Law.* 2017; 57(2):103. doi:10.1177/0025802417704600
717. State of West Virginia Office of the Attorney General, ‘DEA’s Failure to Combat Diversion Cost Lives: results from the West Virginia Attorney General’s Investigation into the DEA’s catastrophic failure to manage the National Drug Quota System from 2010-2016, (June 4, 2020), at p. 3.
718. Stefan G. Kertesz (2017) Turning the tide or riptide? The changing opioid epidemic, *Substance Abuse*, 38:1, 3-8,
719. Steketee JD, et al. Drug wanting: behavioral sensitization and relapse to drug- seeking behavior. *Pharmacol Rev.* 2011 ;63(2):348-365. doi:10.1124/pr.109.001933
720. Steve Mays Linedkin Profile, <https://www.linkedin.com/in/steve-mays-47833336>
721. Steven Rich, Scott Higham and Sari Horwitz *More than 100 Billion Pain Pills Saturated the Nation over Nine Years*, Washington Post, January 14, 2020.
722. Strang J, Babor T, Caulkins J, Fischer B, Foxcroft D, Humphreys K. Drug policy and the public good: evidence for effective interventions. *Lancet.* 2012;379(9810):71-83, at p. 78.
723. Strang, John, et al. "Opioid use disorder." *Nature Reviews Disease Primers* (2020).

*Lembke Report**Confidential — Subject to Protective Order*

724. Strathdee SA, et al. Threading the Needle — How to Stop the HIV Outbreak in Rural Indiana. *N Engl J Med.* 2015. doi:10.1056/NEJMp1507252
725. Strickler, G., et al., Opioid Prescribing Behaviors - prescription Behavior surveillance System, 11 States, 2010-2016. *MMWR Surveill Summ* 2020;69 (1)
726. Subjective Opiate Withdrawal Scale (SOWS) 2017
727. Substance Abuse and Mental Health Service Administration, SAMHSA/HHS: An Update on the Opioid Crisis, March 14, 2018. See https://www.samhsa.gov/sites/default/files/aatod_2018_final.pdf
728. Substance Abuse and Mental Health Services Administration, Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-46, HHS. Publication No. (SMA) 13-4795. Rockville, MD
729. Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A, Stephens K, Chan YF. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. *J Pain.* 2017 Mar;18(3):308-318. doi: 10.1016/j.jpain.2016.11.003. Epub 2016 Nov 28.
730. Sullivan, Mark, et al. Opioid Therapy for Chronic Pain in the US: promises and perils, *Pain.* 2013 December; 154(0 1): S94–100. doi:10.1016/j.pain.2013.09.009
731. Sullivan, Mark, et al. Trends in use of opioids for non-cancer pain conditions 2000–2005 in Commercial and Medicaid insurance plans: The TROUP study, *Journal of the International Association for the Study of Pain* 2008;138(2):440-9
732. Sullivan, MD. Depression Effects on Long-term Prescription Opioid Use, Abuse, and Addiction. *Clin J Pain* (2018)
733. Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. 2016. <https://addiction.surgeongeneral.gov/>.
734. Surratt HL, et al. Prescription opioid abuse among drug-involved street-based sex workers. *J Opioid Manag* 2006;2:283-289
735. Synthetic Opioid Overdose Data, Cts. for Disease Control and Prevention, (Apr. 2, 2019) <https://www.cdc.gov/drugoverdose/data/fentanyl.html>.
736. Taitsman JK, et. al. Commercial Influences on Electronic Health Records and Adverse Effects on Clinical Decision Making. *JAMA Intern Med.* 2020;10.1001/jamainternmed.2020.1318. doi:10.1001/jamainternmed.2020.1318, at p. E1.

*Lembke Report**Confidential — Subject to Protective Order*

737. Tapentadol (CG5503), Clinical Trials.Gov (last updated Apr. 18, 2012), <https://clinicaltrials.gov/ct2/show/NCT00421928>.
738. Taub A. Opioid analgesics in the treatment of chronic intractable pain of non- neoplastic origin. In: Kitahata LM, Collins JD, eds. Narcotic Analgesics in Anesthesiology. Baltimore, MD: Williams & Wilkins; 1982:199–208
739. Tayeb BO, Barreiro AE, Bradshaw YS, Chui KKH, Carr DB. Durations of opioid, non-opioid drug, and behavioral clinical trials for chronic pain: Adequate or inadequate? *Pain Med (United States)*. 2016. doi:10.1093/PM/PNW245, at p. 2043.
740. Taylor CB, Zlutnick SI, Corley MJ, Flora J. The effects of detoxification, relaxation, and brief supportive therapy on chronic pain. *Pain* 1980;8(3):319–29.
741. Taylor v Purdue Pharma et al., No. 504-CV-197, 2005 WL 3308504 (M.D. Georgia 2005)
742. Tennant FS Jr, et al. Narcotic maintenance for chronic pain. Medical and legal guidelines. *Narc Maintenance* 1983; 73:81–94
743. Tennant FS, et al. Chronic opioid treatment of intractable, nonmalignant pain. *NIDA Res Monogr* 1988;81:174–80
744. The Addiction Medicine Foundation, Congressional Briefing – Addiction Medicine: The Urgent Need for Trained Physicians (September 28, 2017), see <https://www.youtube.com/watch?v=y6kBoQckmHw>
745. The California “Intractable Pain Law” (Pain Patient’s Bill of Rights) provides good language on how patients have a right to opioids for chronic pain. https://leginfo.legislature.ca.gov/faces/codes_displayText.xhtml?lawCode=HSC&division=106.&title=&part=4.5.&chapter=&article=
746. The Heller School of Social Policy and Management, Briefing on PDMP Effectiveness. Center of Excellence Brandeis University. www.pdmpexcellence.org.
747. The Joint Commission (Patient Safety Advisory Group), Safe use of opioids in hospitals. Sentinel Event Alert Issue 49. http://www.jointcommission.org/sea_issue_49/.
748. The Joint Commission. <http://www.jointcommission.org/>. Accessed September 2, 2015
749. The Journal of Pain Abstracts Presented at the 32nd Annual Scientific Meeting of the American Pain Society. American Pain Society 08 May 2013 - 11 May 2013

750. The National Academies Press, Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use, Washington, DC: The National Academies Press. doi: 10.17226/24781
751. Thiels CA, *et al.* Chronic use of tramadol after acute pain episode: cohort study. *BMJ* 2019;365: |1849, 1-10 at pp. 5-6.
752. Thornton, J. Douglas, et al. "Health-related quality of life in patients receiving long-term opioid therapy: a systematic review with meta-analysis." *Quality of Life Research* 26.8 (2017): 1955-1967. [including supplementary materials]
753. Todd, Knox H. A Review of Current and Emerging Approaches to Pain Management in the Emergency Department, *Pain Ther*, 2017; 6; 193-202
754. Todd, Roxy. "Inside West Virginia's Overwhelmed Foster Care System" *WV Public Broadcasting* October 9, 2019 <https://www.wvpublic.org/post/inside-west-virginia-s-overwhelmed-foster-care-system#stream/0>
755. Tolia VN, *et al.* Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *N Engl J Med.* 2015 May 28;372(22):2118-26. doi:10.1056/NEJMsa1500439. Epub 2015 Apr 26.
756. Tolia VN, Patrick SW, Bennett MM, *et al.* Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *Obstet Gynecol Surv.* 2015. doi:10.1097/OGX.0000000000000243, at p. 2118.
757. Townsend CO, Kerkvliet JL, Bruce BK, *et al.* A longitudinal study of the efficacy of a comprehensive pain rehabilitation program with opioid withdrawal: Comparison of treatment outcomes based on opioid use status at admission. *Pain* 2008;140 (1):177–89.
758. Transcript of Lecture UCSF Surgery Grand Rounds 9/7/2016, from link
<https://lecture.ucsf.edu/ets/Play/a7a1b5e958cf491da5084cd386d1c74a1d?catalog=82b316ca-6cfa-4fcf-9a6b-1c2a3f9eef3b> (transcribed 2020-02-13)
759. Trouvin AP, Berenbaum F, Perrot S, The Opioid Epidemic: helping rheumatologists prevent a crisis. *RMD Open* (2019)
760. Turner, J.A, *et al.* Drug utilization patterns in chronic pain patients. *Pain* 1982; 12:357-363
761. Turturro MA, Paris PM, Larkin GL. Tramadol versus hydrocodone-acetaminophen in acute musculoskeletal pain: a randomized, double-blind clinical trial. *Annals of emergency medicine*. 1998; 32(2):139-43. [pubmed]

*Lembke Report**Confidential — Subject to Protective Order*

762. U.S. Department of Health and Human Services. *Clinical Decision Support*. (April 10, 2018). <https://www.healthit.gov/topic/safety/clinical-decision-support>
763. U.S. Food & Drug Administration. CELEBREX (celecoxib capsules drug label. *Drugs@FDA: FDA-Approved Drugs*. At https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020998s017lbl.pdf
764. U.S. Food & Drug Administration. VIOXX (rofecoxib tablets and oral suspension) drug label. *Drugs@FDA: FDA-Approved Drugs*. At https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21647_vioxx_lbl.pdf
765. United States Dep't of Health and Human Servs. *Addressing Prescription Drug Abuse in the United States*. 1-36, at pp., 9-10, https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf.
766. United States Department of Health and Human Services. Addressing Prescription Drug Abuse in the United States. :1-36, at p. 16. *See* https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf.
767. United States Department of Health and Human Services. *HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-term Opioid Analgesics*. (Oct. 2019); https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf.
768. United States Department of Justice. "Electronic Health Records Vendor to Pay \$145 Million to Resolve Criminal and Civil Investigations." *Justice News*. January 27, 2020. [At justice.gov/opa/pr/electronic-health-records-vendor-pay-145-million-resolve-criminal-and-civil-investigations-0](https://justice.gov/opa/pr/electronic-health-records-vendor-pay-145-million-resolve-criminal-and-civil-investigations-0)
769. United States Government Accountability Office. "Report to Congressional Requesters. Medicare Part D: Instances of Questionable Access to Prescription Drugs." September 2011. GAO-11-699.
770. United States of America v. Practice Fusion, Inc. Case No. 2:20-cr-11-1. United States District Court for the District of Vermont.
771. UNODC. World Drug Report. United Nations Publication, Sales No. E.12.XI.1; 2012.
772. Urban BJ, et al. Long-term use of narcotic/antidepressant medication in the management of phantom limb pain. Pain 1986; 24:191–6
773. US Department of Justice. *Electronic Health Records Vendor to Pay \$145 Million to Resolve Criminal and Civil Investigations* (January 27, 2020).

<https://www.justice.gov/opa/pr/electronic-health-records-vendor-pay-145-million-resolve-criminal-and-civil-investigations-0>

774. US. Government Accountability Office. (2011, September). Medicare Part D: Instances of questionable access to prescription drugs, (Publication No. GAO-11-699) at p. 11, <https://www.gao.gov/new.items/d11699.pdf>,
775. Vaglienti RM, et al. Misuse of prescribed controlled substances defined by urinalysis. WV Med J 2003; 99:67–70.
776. Van Zee, Art. The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy, American Journal of Public Health 2009; 99(2): 221–227
777. Vanderlip ER, et al. National study of discontinuation of long-term opioid therapy among veterans. Pain. 2014 Dec; 155(12):2673-9. doi: 10.1016/j.pain.2014.09.034. Epub 2014 Sep 30. PMID: 25277462 Free PMC Article
778. VanHouten JP, et al. Drug Overdose Deaths Among Women Aged 30–64 Years—United States, 1999–2017. MMWR Morb Mortal Wkly Rep. 2019;68(1):1-5. doi:10.15585/mmwr.mm6801a1
779. Varela A. The Relationship between Psychosocial Factors and Reported Disability: the role of pain self-efficacy. Capella University PhD Dissertation (2019)
780. Velly, AM, Mohit S. Epidemiology of Pain and Relation to Psychiatric Disorders. Progress in Neuropsychopharmacology & Biological Psychiatry (2018)
781. Venkataramani, Atheendar S., et al. "Association Between Automotive Assembly Plant Closures and Opioid Overdose Mortality in the United States: A Difference-in-Differences Analysis." JAMA Internal Medicine (2019).
782. Vila HJ, et al. The efficacy and safety of pain management before and after implementation of hospital-wide pain management standards: is patient safety compromised by treatment based solely on numerical pain ratings? Anesth Analg. 2005; 101:474–480.
783. Vioxx label (2004), *see* https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21647_vioxx_lbl.pdf at p. 3
784. Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999–2008; MMWR, November 4, 2011 / 60(43);1487-1492.

*Lembke Report**Confidential — Subject to Protective Order*

785. Vivolo-Kantor AM, Seth P, Gladden RM, *et al.* Vital Signs: Trends in Emergency Department Visits for Suspected Opioid Overdoses — United States, July 2016–September 2017. *MMWR Morb Mortal Wkly Rep.* 2018;67:279–285, at p. 281.
786. Voelker, Rebecca MSJ. A Mandate for Opioid Education?, *JAMA*, 2018; 319(19); 1974.
787. Volkow N, Jones E, Einstein E, Wargo E. Prevention and Treatment of Opioid Misuse and Addiction: a review. *JAMA Psychiatry* (2019)
788. Volkow ND, et al. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry*. 2004;9(6):557-569.
doi:10.1038/sj.mp.4001507
789. Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain - Misconceptions and Mitigation Strategies. *N Engl J Med.* 2016;374(13):1253-1263.
doi:10.1056/NEJMra1507771, at p. 1254.
790. Volkow, N., et al. Opioid Abuse in Chronic Pain - Misconceptions and Mitigation Strategies , *N Engl J Med* 2016;374:1253-63
791. Volkow, Nora D., George F. Koob, and A. Thomas McLellan. Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine* 374.4 (2016): 363-371.
792. Volkow, Nora D., J. S. Fowler, and G-J. Wang. Role of dopamine in drug reinforcement and addiction in humans: results from imaging studies. *Behavioural pharmacology* 13.5 (2002): 355-366.
793. Vorsanger G, et al., Post hoc analysis of a randomized, double-blind placebo-controlled efficacy and tolerability study of tramadol extended release for the treatment of osteoarthritis pain in geriatric patients. *Clin Ther* 2007; 29:2520-2535, at p. 2530.
794. Vosburg, Suzanne K., et al. Assessment of tapentadol API abuse liability with the researched abuse, diversion and addiction-related surveillance system. *The Journal of Pain* 19.4 (2018): 439-453.
795. Vosburg, Suzanne K., et al. Evaluation of Abuse and Route of Administration of Extended-Release Tapentadol Among Treatment-Seeking Individuals, as Captured by the Addiction Severity Index–Multimedia Version (ASI-MV). *Pain Medicine* (2019).
796. Vowles KE., et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. 2015 Apr; 156(4):569-76. doi: 10.1097/01.j.pain.0000460357.01998.f1.

797. Wakeland W, Nielsen A, and Geissert P. Dynamic Model of Nonmedical Opioid Use Trajectories and Potential Policy Interventions. *Am J Drug Alcohol Abuse*. 2015; 41(6):508-518.
798. Wallin CM. Gestational Opioid Exposure: effects on pregnancy, NAS, maturation & behavioral development. Wayne State University Masters Dissertation (2019)
799. Wan Lu C, Long-term use of narcotic analgesics in chronic pain, *Soc Sci Med* 1988; 19:1379-82.
800. Warner M, et al. Drug poisoning deaths in the United States, 1980–2008. NCHS data brief, no 81 Hyattsville, MD US Dep Heal Hum Serv CDC. 2011.
801. Wasan A, et al. Iatrogenic addiction in patients treated for acute or subacute pain: a systematic review. *J Opioid Manage* 2006;2(1):16-22.
802. Wasan AD, et al. Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients? *Clin J Pain* 2009;25:193–8.
803. Watson C. Efficacy of oxycodone in neuropathic pain: A randomized trial in postherpetic neuralgia, *Neurology* 1998; 50 (6):1837-1841.
804. Watson CPN. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy, *Pain* 2003; 105: 71-78
805. Wazana, A. Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?, *JAMA*. 2000; 283(3):373-380
806. Webster LR, et al. Predicting aberrant behaviors opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med* 2005; 6: 432–43.
807. Webster LR, Pain and Suicide: the other side of the opioid story. *Pain Medicine* 2014; 15: 345–346
808. Webster LR. Risk Factors for Opioid-Use Disorder and Overdose. *Anesth Analg*. 2017 Nov; 125(5):1741-1748. doi: 10.1213/ANE.0000000000002496.
809. Weimer MB, et al. A chronic opioid therapy dose reduction policy in primary care. *Subst Abus*. 2016;37(1):141-7
810. Weisner CM, et al. Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. *Pain*. 2009; 145(3):287–293.

*Lembke Report**Confidential — Subject to Protective Order*

811. Weissman DE, et al. Opioid pseudoaddiction--an iatrogenic syndrome. *Pain*. 1989 Mar;36(3):363-6.PMID:2710565
812. Welsch, et al. Opioids in chronic noncancer pain—are opioids superior to nonopioid analgesics? A systematic review and meta-analysis of efficacy, tolerability and safety in randomized head-to-head comparisons of opioids versus nonopioid analgesics of at least four week's duration. *Schmerz* 2015 Feb;29(1):85-95. doi: 10.1007/s00482-014-1436-0.
813. West Virginia Attorney General, “Best Practices for Prescribing Opioids in West Virginia,” pp. 1, 2, <http://ago.wv.gov/Documents/2016.08.19%20BP%20Prescribing.PDF>. (emphasis added.)
814. West Virginia Board of Pharmacy Prescription Opioid Problematic Prescribing Indicators County Report: Cabell County Final Report
https://helpandhopewv.org/docs/PFS_County_Reports/Cabell_PfS%20County%20Report_s_Final.pdf
815. West Virginia Coalition on Chronic Pain Management. 2019 Report to the Legislature
816. West Virginia Drug Overdose Deaths Historical Overview 2001-2015, West Virginia Department of Health and Human Resources, August 17, 2017, at p.7, https://dhhr.wv.gov/oeps/disease/ob/documents/opioid/wv-drug-overdoses-2001_2015.pdf.
817. West Virginia Drug Overdose Deaths Historical Overview 2001-2015, West Virginia Department of Health and Human Resources, August 17, 2017, at p.9, https://dhhr.wv.gov/oeps/disease/ob/documents/opioid/wv-drug-overdoses-2001_2015.pdf.
818. West Virginia Legislature - SB 339
819. West Virginia Violence and Injury Prevention Center. (2017) West Virginia Drug Overdose Deaths in 2016: Healthcare Systems Utilization, Risk Factors, and Opportunities for Intervention
820. Wild JE, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Practice* 2010; 10:416-427
821. Wilder-Smith CH. Treatment of severe pain from osteoarthritis with slow-release tramadol or dihydrocodeine in combination with NSAID's: a randomized study comparing analgesia, antinociception and gastrointestinal effects. *Pain* 2001; 91: 23-31.

822. Wildes M, Bigand T, Layton M, Wilson M. Cannabis Use and Cognition in Adults Prescribed Opioids for Persistent Pain. *Pain Management Nursing* (2019)
823. Williams v Purdue Pharma et al. No. 4:04CV02407 (S.D. Texas 2006), produced at PKY182921037
824. Wilsey BL, et al. Psychological comorbidities predicting prescription opioid abuse among patients in chronic pain presenting to the emergency department. *Pain Med* 2008; 9:1107–17.
825. Wise R, et al. The development and maintenance of drug addiction. *Neuropsychopharmacology*. 2014;39(2):254–262.
826. World Health Organization, CIOMS, http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf, at p. 10.
827. World Health Organization, Hierarchy of rare-uncommon-common events. Who. May 8, 2017. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourse s/definitions.pdf
828. Wu SM, et al. The addiction behaviors checklist: validation of a new clinician- based measure of inappropriate opioid use in chronic pain. *J Pain Symptom Manage* 2006; 32:342–51.
829. WV Code § 30-3A-2 (1998), Limitation on disciplinary sanctions or criminal punishment related to management of intractable pain, http://www.wvlegislature.gov/Bill_Text_HTML/1998_SESSONS/RS/Bills/HB4058%20ENR.htm.
830. WV Code § 30-3A-2 (2012), available at <http://www.wvlegislature.gov/wvcode/Code.cfm?chap=30&art=3A>
831. WV Overdoses 2001-2018 Selected Drugs Data Set www.dhhr.wv.gov/bph
832. Yeoh, S., et al. Cognitive and Motor Outcomes of Children With Prenatal Opioid Exposure A Systematic Review and Meta-analysis. *JAMA Network Open*. 2019;2(7):
833. Yeoh, Su Lynn, et al. Online comments on "Cognitive and motor outcomes of children with prenatal opioid exposure: a systematic review and meta-analysis." *JAMA network open* 2.7 (2019): e197025-e197025.

*Lembke Report**Confidential — Subject to Protective Order*

834. Yeoh, Su Lynn, et al. Supplementary Online Content "Cognitive and motor outcomes of children with prenatal opioid exposure: a systematic review and meta-analysis." *JAMA network open* 2.7 (2019): e197025-e197025.
835. Younger J, Barelka P, Carroll I, et al. Reduced cold pain tolerance in chronic pain patients following opioid detoxification. *Pain Med* 2008;9(8):1158–63
836. Ytterberg SR. Codeine and oxycodone use in patients with chronic rheumatic disease pain. *Arthritis & Rheumatism* 1998; 41 (9):1603-1612.
837. Zaman T, Rife T, Batki S, Pennington DL. An Electronic Intervention to Improve Safety for Pain Patients Co-Prescribed Chronic Opioids and Benzodiazepines. *Substance Abuse* (2018)
838. Zaveri, Shruti, et al. Risk of Chronic Opioid Use in Opioid-Naïve and Non-Naïve Patients after Ambulatory Surgery. *Journal of Gastrointestinal Surgery* (2019): 1-7.
839. Zeng C, et al. Association of tramadol with all-cause mortality among patients with osteoarthritis. *JAMA* 2019;321(10):969-982, at p. 969.
840. Zenz M, et al. Long-term oral opioid therapy in patients with chronic nonmalignant pain. *J Pain Symptom Manage* 1992;7:69–77
841. Zhu - Initial Opioid Prescriptions among U.S. Commercially Insured Patients, 2012–2017. *n engl j med* 380;11. 1043-52
842. Zimmerman M. Individual aspects of the quality of life of patients with chronic pain. Observational study of treatment with fentanyl-TTS, *MMW Fortschritte der Medizin* 2005; 147 (Suppl 1):33-40.
843. Zimmermann M. History of pain treatment from 1500 to 1900, *Schmerz*. 2007; 21(4):297–306.
844. "Drug abuse in Egypt: A pill for work and play." *The Economist*. April 18, 2015. (2015 WLNR 11173652)
845. "Distribution of opioids by different types of medicare prescribers" Google Scholar Results
https://scholar.google.com/scholar?cites=3449278328675579417&as_sdt=2005&sciodt=0,5&hl=en (last accessed April 14, 2020)
846. "Drug Dealer Admits to Giving Free Sample." *The Herald Dispatch* https://www.herald-dispatch.com/news/drug-dealer-admits-to-giving-free-sample/article_ce289f74-e9c3-58ce-8cce-d7483e774627.html

Lembke Report

Confidential — Subject to Protective Order

All Expert Witness reports and supplements from MDL 2804 served on March 25, 2019 and May 10, 2019 as well as materials identified within.

All Expert Witness reports from the NY Opioid Litigation 400000/2017 served on December 19, 2019 and February 3rd, 2020 as well as materials identified within.

All Expert Witness reports from Cabell County Commission and City of Huntington, West Virginia, (The Cabell Huntington Community) v. AmerisourceBergen Drug Corporation, Cardinal Health, Inc., and McKesson Corporation served on August 3, 2020 as well as materials identified within.

All items referenced in Dr. Lembke's expert witness reports or listed on Materials Considered lists.

BATES DOCUMENTS

- 847. ABDCMDL00002828
- 848. ABDCMDL00269293
- 849. ABDCMDL00323380-ABDCMDL00323439
- 850. ABDCMDL00532594
- 851. ABDCMDL00532649
- 852. ABDCMDL00569571
- 853. ABDCMDL05775790
- 854. ABDCMDL05795672
- 855. ACTAVIS0006823
- 856. ACTAVIS0220239
- 857. ALLERGAN_MDL_00007268- 312
- 858. ALLERGAN_MDL_00026506-52
- 859. ALLERGAN_MDL_01052119-465
- 860. ALLERGAN_MDL_01237743-62
- 861. ALLERGAN_MDL_01361692

*Lembke Report**Confidential — Subject to Protective Order*

- 862. ALLERGAN_MDL_01741588- 639
- 863. ALLERGAN_MDL_03733544
- 864. CAH_MDL2804_00132701
- 865. CAH_MDL2804_00132726
- 866. CAH_MDL2804_00133350
- 867. CHHD_0000871
- 868. CHHD_0000871
- 869. CHHD_0005048
- 870. CHI_001222272-87
- 871. E01_00015979
- 872. END00099670-71
- 873. END00474717
- 874. ENDO-CHI_LIT-00053284-35
- 875. ENDO-CHI_LIT-00210473-76
- 876. ENDO-CHI_LIT-00237187
- 877. ENDO-CHI_LIT-00294169-ENDO-CHI_LIT-00294178
- 878. ENDO-CHI_LIT-00541205
- 879. ENDO-CHI_LIT-00541211
- 880. ENDO-OPIOID MDL-03850803
- 881. ENDO-OPIOID_MDL-01407115
- 882. ENDO-OPIOID_MDL-02002494
- 883. ENDO-OPIOID_MDL-02002495
- 884. ENDO-OPIOID_MDL-02212377-392

Lembke Report

Confidential — Subject to Protective Order

- 885. ENDO-OPIOID_MDL-03739179
- 886. ENDO-Opioid_MDL-04929187
- 887. ENDO-OPIOID_MDL-05550271
- 888. ENDO-OR-CID-00418114-ENDO-OR-CID-00418117
- 889. ENDO-OR-CID-00772464-65
- 890. Excerpt of PKY183320282
- 891. PKY183320390-PKY183320395
- 892. JAN00222151
- 893. JAN00222296
- 894. JAN-MS-00000001
- 895. JAN-MS-00000002
- 896. JAN-MS-00000306
- 897. JAN-MS-00015864
- 898. JAN-MS-00016372-97
- 899. JAN-MS-00068759-828
- 900. JAN-MS-00106322
- 901. JAN-MS-00238338-45
- 902. JAN-MS-00287030
- 903. JAN-MS-00302787
- 904. JAN-MS-00303825
- 905. JAN-MS-00306713
- 906. JAN-MS-00310227
- 907. JAN-MS-00310473

Lembke Report

Confidential — Subject to Protective Order

- 908. JAN-MS-00313080
- 909. JAN-MS-00313196
- 910. JAN-MS-00362490
- 911. JAN-MS-00402671
- 912. JAN-MS-00476031
- 913. JAN-MS-00481055
- 914. JAN-MS-00653403
- 915. JAN-MS-00653426
- 916. JAN-MS-00704213
- 917. JAN-MS-00779345
- 918. JAN-MS-00785752
- 919. JAN-MS-00785795
- 920. JAN-MS-00829901
- 921. JAN-MS-00864412
- 922. JAN-MS-00890573
- 923. JAN-MS-00924772
- 924. JAN-MS-00924775
- 925. JAN-MS-01019418
- 926. JAN-MS-01071368
- 927. JAN-MS-01071368-JAN-MS-01071428
- 928. JAN-MS-01135846
- 929. JAN-MS-01238002
- 930. JAN-MS-01509021

Lembke Report

Confidential — Subject to Protective Order

- 931. JAN-MS-02757826
- 932. JAN-MS-02971159
- 933. JAN-MS-03071350
- 934. JAN-TX-00001492
- 935. JAN-TX-00002318
- 936. JAN-TX-00005143
- 937. JAN-TX-00015731
- 938. JAN-TX-00022608
- 939. JAN-TX-00053505
- 940. JAN-TX-00059363
- 941. JAN-TX-00066294
- 942. JAN-TX-00068278
- 943. JAN-TX-00098902
- 944. JAN-TX-00277836
- 945. JAN-TX-00319956
- 946. MCKMDL00334317
- 947. MCKMDL00334324
- 948. MCKMDL00334328
- 949. MCKMDL00353277
- 950. MCKMDL00353277-MCKMDL00353278
- 951. MCKMDL00353279-MCKMDL00353280
- 952. MCKMDL00353282-MCKMDL00353283
- 953. MCKMDL00353307

Lembke Report

Confidential — Subject to Protective Order

- 954. MCKMDL00353368
- 955. MCKMDL00353368-MCKMDL00353369
- 956. MCKMDL00385864
- 957. MCKMDL00726854-MCKMDL00726884
- 958. MDL_RWJF_0000001
- 959. MDL_RWJF_0000003
- 960. MDL_RWJF_0000004
- 961. MDL_RWJF_0000005
- 962. MDL_RWJF_0000009
- 963. MDL_RWJF_0000010
- 964. MDL_RWJF_0000012
- 965. MDL_RWJF_0000013
- 966. MNK-T1_0000098099
- 967. MNK-T1_0000098925-26
- 968. MNK-T1_0000529044-126
- 969. MNK-T1_0000607120-21
- 970. MNK-T1_0000626241-69
- 971. MNK-T1_0000917000
- 972. MNK-T1_0001279950
- 973. MNK-T1_0001347664-93
- 974. MNK-T1_0001531482
- 975. MNK-T1_0001531484
- 976. MNK-T1_0001786857

Lembke Report

Confidential — Subject to Protective Order

- 977. MNK-T1_0001786865
- 978. MNK-T1_0002159712
- 979. MNK-T1_0002183036
- 980. MNK-T1_0002183040
- 981. MNK-T1_0002248914
- 982. MNK-T1_0002248919
- 983. MNK-T1_0002315694
- 984. MNK-T1_0005981734-MNK-T1_0005981750
- 985. MNK-T1_0006127321-83
- 986. MNK-T1_0006632298
- 987. MNK-T1_0007201839
- 988. MNK-T1_0007819281
- 989. MNK-T1_0007819281-MNK-T1_0007819282
- 990. MNK-T1-0007808356
- 991. PDD1501814066
- 992. PDD1701396088-118
- 993. PDD1701481531
- 994. PDD1706042217
- 995. PDD1706189266
- 996. PDD1706189902-04
- 997. PDD8003102640
- 998. PDD8013002926
- 999. PDD801303375

Lembke Report

Confidential — Subject to Protective Order

- 1000. PDD8023035114-60
- 1001. PDD8023045826-945
- 1002. PDD8801126680-81
- 1003. PDD8801183361-64
- 1004. PDD8806011994-2069
- 1005. PDD9521403001
- 1006. PDD9521403491 - PDD9521403495
- 1007. PKY180170528-653
- 1008. PKY180435433-707
- 1009. PKY180625450-745
- 1010. PKY180769094-535
- 1011. PKY180775599-707
- 1012. PKY180796628-PKY180796639
- 1013. PKY180947673-701
- 1014. PKY181246683-7419
- 1015. PKY181654940-82
- 1016. PKY181654950
- 1017. PKY181655057-139
- 1018. PKY181655140-233
- 1019. PKY181655155
- 1020. PKY181655160
- 1021. PKY181884704-751
- 1022. PKY181889263-9806

Lembke Report

Confidential — Subject to Protective Order

- 1023. PKY182921037-PKY182921073.
- 1024. PKY183063227
- 1025. PKY183220480-0558
- 1026. PKY183320282
- 1027. PLTF_2804_000003844
- 1028. PPLP003337352
- 1029. PPLP003370086
- 1030. PPLP003478540
- 1031. PPLP003478540-PPLP003478553
- 1032. PPLP003517021-042
- 1033. PPLP003877439
- 1034. PPLP004058443
- 1035. PPLP004345894
- 1036. PPLPC002000140782
- 1037. PPLPC002000140782-PPLPC002000140783
- 1038. PPLPC004000146529-PPLPC004000146531
- 1039. PPLPC009000022561
- 1040. PPLPC012000475869 - PPLPC012000475883
- 1041. PPLPC013000017513
- 1042. PPLPC016000255303
- 1043. PPLPC017000046138
- 1044. PPLPC017000453148-49
- 1045. PPLPC017000514276

Lembke Report

Confidential — Subject to Protective Order

- 1046. PPLPC017000564601
- 1047. PPLPC018000201219
- 1048. PPLPC018000252189
- 1049. PPLPC018000784990-91
- 1050. PPLPC019000790159
- 1051. PPLPC031000385886
- 1052. PPLPC031000425439
- 1053. PPLPC031001481881-PPLPC031001481890
- 1054. PPLPC032000262924
- 1055. PPLPC045000004928-33
- 1056. PURCHI-003286781-881
- 1057. SUMMIT_002103849
- 1058. SUMMIT_002103858
- 1059. TEVA_AAMD_00791885
- 1060. TEVA_CAOC_00759630
- 1061. TEVA_MDL_A_09667462
- 1062. TEVA_MDL_A_00890304
- 1063. TEVA_MDL_A_01327080
- 1064. TEVA_MDL_A_02401119
- 1065. TEVA_MDL_A_04313917
- 1066. TEVA_MDL_A_09062111
- 1067. WIS_PPSG_000026
- 1068. WIS_PPSG_000036

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1069. WIS_PPSG_002042

1070. WIS_PPSG_008292

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Anna Lembke, M.D. Report

EXHIBIT C

Statement of Compensation Rate

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Anna Lembke, M.D.
Stanford University School of Medicine
Department of Psychiatry and Behavioral Sciences

Expert Witness Fee Schedule: Case No. 1:17-op-45053-DAP and No. 1:17-op-45054 Opioid Litigation

Work	Details	Fee
Preliminary Work	Telephone conferences, record review, report writing, and travel	\$500 per hour
Court Work	Court appearances and depositions	\$800 per hour
Expenses	Travel and other reasonable out-of-pocket expenses	Reimbursement

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Anna Lembke, M.D. Report

EXHIBIT D

Prior Testimony

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Stanford University School of Medicine
Department of Psychiatry and Behavioral Sciences

Prior Testimony

1. *People v. Philip Morris Ingram*, (Cal. Sup. Ct., Docket 62-144622)
2. *National Prescription Opiate Litigation*, MDL No. 2804
(N.D. Ohio, Case 1:17-md-2804)
3. *In Re Opioid Litigation*, (Suffolk County, New York Supreme Court, Index No. 400000/2017), relating to Case Nos. County of Suffolk, 400001/2017; County of Nassau, 400008/2017; and New York State, 400016/2018